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Conventional occlusion versus pharmacologic penalization for amblyopia (Review)

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[Intervention Review]

Conventional occlusion versus pharmacologic penalization for amblyopia

Tianjing Li[1], Riaz Qureshi[1], Kate Taylor[2]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. [2]Department of Ophthalmology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Contact address: Tianjing Li, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, E6011, Baltimore, Maryland, 21205, USA. tli19@jhu.edu.

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ABSTRACT

Background

Amblyopia is defined as impaired visual acuity in one or both eyes without demonstrable abnormality of the visual pathway, and is not immediately resolved by wearing glasses.

Objectives

In performing this systematic review, we aimed to synthesize the best available evidence regarding the effectiveness and safety of conventional occlusion therapy compared to atropine penalization in treating amblyopia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2018, Issue 8); Ovid MEDLINE; Ovid Embase; LILACS BIREME; ClinicalTrials.gov; ISRCTN; and the WHO ICTRP on 7 September 2018.

Selection criteria

We included randomized/quasi-randomized controlled trials comparing conventional occlusion to atropine penalization for amblyopia.

Data collection and analysis

Two review authors independently screened abstracts and full-text articles, abstracted data, and assessed risk of bias.

Main results

We included seven trials (five randomized controlled trials and two quasi-randomized controlled trials) conducted in six countries (China, India, Iran, Ireland, Spain, and the United States) with a total of 1177 amblyopic eyes. Three of these seven trials were from the original 2009 version of the review. We assessed two trials as having a low risk of bias across all domains, and the remaining five trials as having unclear or high risk of bias for some domains.

As different occlusion modalities, atropine penalization regimens, and populations were used across the included trials, we did not conduct any meta-analysis due to clinical and statistical heterogeneity. Evidence from six trials (two at low risk of bias) suggests that atropine penalization is as effective as conventional occlusion in improving visual acuity. Similar improvement in visual acuity was reported at all time points at which it was assessed, ranging from five weeks (improvement of 1 line) to 10 years (improvement of greater than 3 lines). At six months, although most participants (363/522) come from a trial rated as at low risk of bias with a precise estimate (mean difference (MD) 0.03, 95% confidence interval (CI) 0.00 to 0.06), two other trials rated as at high risk of bias produced inconsistent estimates and wide

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confidence intervals (MD −0.02, 95% CI −0.11 to 0.07 and MD −0.14, 95% CI −0.23 to −0.05; moderate-certainty evidence). At 24 months, additional improvement was found in both groups, but there continued to be no meaningful difference between those receiving occlusion and those receiving atropine therapies (moderate-certainty evidence).

We did not find any difference in ocular alignment, stereo acuity, or sound eye visual acuity between occlusion and atropine penalization groups (moderate-certainty evidence). Both treatments were well tolerated. Atropine was associated with better adherence (moderate-certainty evidence) and quality of life (moderate-certainty evidence), but also a higher reported risk of adverse events in terms of mild reduction in the visual acuity of the sound eye not requiring treatment and light sensitivity (high-certainty evidence). Skin, lid, or conjunctival irritation were more common among participants receiving patching than those receiving atropine (high-certainty evidence). Atropine penalization costs less than conventional occlusion.

Authors' conclusions

Both conventional occlusion and atropine penalization produce visual acuity improvement in the amblyopic eye. Atropine penalization appears to be as effective as conventional occlusion, although the magnitude of improvement differed among the trials we analyzed.

PLAIN LANGUAGE SUMMARY

Treatment of amblyopia (lazy eye) with patching or drops/drug treatment

What is the aim of this review?
In this systematic review, we aimed to summarize the best available evidence regarding the effectiveness and safety of conventional occlusion (patching) and atropine penalization (drops) as treatments for amblyopia (lazy eye).

Key messages
We found evidence suggesting that conventional patching and atropine drops led to similar improvement in vision.

What was studied in the review?
Amblyopia (lazy eye) is a common childhood condition and is defined as poor vision in one or both eyes. Lazy eye is present with no clear problems with the visual pathway and is not immediately fixed by wearing glasses. Treatment for lazy eye usually starts with prescribing necessary glasses to correct any optical defects followed by promoting the use of the lazy (weaker) eye. This systematic review compared two treatments used to promote the use of the weaker eye: covering the stronger eye for a set number of hours per day, and atropine drops (atropine sulphate) to blur the eyesight of the better-seeing eye.

What are the main results of the review?
Our update of the previous version of this review included seven trials with a total of 1177 amblyopic eyes. Evidence from six trials (two of good methodological quality) suggests both patching and atropine drops produce visual acuity improvement in the short term (one to six months) and long term (24 months) in the weaker eye after starting treatment. We found no differences between the two treatments in straightening of the eyes, depth perception, or vision in the better eye. Both treatments were well tolerated. Atropine drops were taken more regularly than using the patch and associated with better quality of life, but blurry vision and sensitivity to light was more common in the atropine treated eyes. Skin, lid, or conjunctival irritation were more common among participants receiving patching than those receiving atropine.

How up-to-date is this review?
This review is up-to-date as of 7 September 2018.

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Summary of findings for the main comparison. Conventional occlusion compared to atropine penalization for amblyopia

Conventional occlusion compared to atropine penalization for amblyopia

Patient or population: Participants of any age with either unilateral strabismic, anisometropic, or mixed (strabismic-refractive) amblyopia; deprivation amblyopia was not included
Intervention: Conventional occlusion (patching) of any type (part time or full time, total adhesive, partial occlusion, optical penalization, shield, and pirate patch)
Comparison: Atropine penalization (eye drops) with or without conventional occlusion

Setting: Outpatient

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Mean visual acuity at 6 months (difference in LogMAR units between occlusion and atropine groups) Assessed with Amblyopia Treatment Study visual actuity testing procotol, Early Treatment Diabetic Retinopathy Study chart, or LogMAR Crowded Glasgow acuity cards.	Not combined	-	552 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Although most participants (363/522) come from a trial rated as at low risk of bias with a precise estimate (MD 0.03, 95% CI 0.00 to 0.06) (PEDIG 2002), 2 other trials rated as at high risk of bias produced inconsistent estimates and wide confidence intervals (MD −0.02, 95% CI −0.11 to 0.07; and MD −0.14, 95% CI −0.23 to −0.05) (Menon 2008; Tejedor 2008).
Mean visual acuity at 24 months (difference in LogMAR units between occlusion and atropine groups) Assessed with Amblyopia Treatment Study visual actuity testing procotol or E chart.	Not combined	-	483 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	1 trial rated as at low risk of bias provides a precise estimate (MD 0.01, 95% CI −0.02 to 0.04) (PEDIG 2002), but no estimate of effect could be derived from Medghalchi 2011, reducing our certainty in this outcome at 24 months.
Adherence to treatment (different measures and time points reported in the included studies)	Not combined	-	588 (4 RCTs)	⊕⊕⊕⊖ MODERATE [2]	There did appear to be some evidence that atropine penalization was associated with significantly better ad-

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Assessed at different time points (6, 12, 0r 24 months), and with different measures (percentage of prescribed treatment that was completed at each study visit, peeking over the glasses, adherence rated by parents, or by the number of days missing treatment).					herence than conventional occlusion (PEDIG 2002; Foley-Nolan 1997). Menon 2008 and Tejedor 2008 found no difference in adherence between groups.
Ocular alignment (different measures and time points reported in the included studies) Assessed at different time points (17 weeks, 24 months, or cessation of treatment) and by the proportions of participants who developed strabismus, showed changes in pre-existing strabismus, or had an increase/decrease of strabismus degree 8△ or more.	Not combined	-	888 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3]	PEDIG 2002 and PEDIG 2008 reported no evidence of difference in the number of participants in each treatment group who developed strabismus or showed changes in pre-existing strabismus. Yan 2008 found no differences in the risks of increased or decreased strabismus degree of 8△ or more.
Stereo acuity (different measures and time points reported in the included studies) Assessed at different time points (17 weeks, 6 months, 2 years, or at cessation of treatment) and using different measures (TNO stereo test, Titmus fly test, Randot preschool stereo acuity test, or Randot circles stereo acuity test).	Not combined	-	865 (5 RCTs)	⊕⊕⊕⊖ MODERATE [2]	None of the trials (PEDIG 2002, PEDIG 2008, Medghalchi 2011, Menon 2008, Tejedor 2008) reported statistical differences in stereo acuity achieved between groups.
Quality of life (different measures and time points reported in the included studies) Assessed at different time points (17 weeks or 6 months) by patient preference or the Amblyopia Treatment Index questionnaire.	Not combined	-	256 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	Menon 2008 reported participant preference for atropine due to cosmetic and psychological reasons; however, the difference between groups was not statistically significant. PEDIG 2008 investigators administered Amblyopia Treatment Index questionnaires to parents of participants. Although scores were comparable between patching and atropine groups for the adverse events subscale, parents favored atropine for the social stigma and adherence subscales.

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Adverse events (reported occurrence of: mild reduction in the visual acuity of the sound eye not requiring treatment; light sensitivity; skin, lid, or conjunctival irritation) Assessed at different time points (17 weeks or 2 years).	Not combined	-	612 (2 RCTs)	⊕⊕⊕⊕ HIGH	PEDIG 2002 reported that the proportion of participants experiencing mild reduction in visual acuity of the sound eye not requiring treatment was 3 times higher among those in the atropine group as compared with the patching group. Both PEDIG 2002 and PEDIG 2008 reported light sensitivity among participants in the atropine group but not the patching group. Both PEDIG 2002 and PEDIG 2008 reported that irritation (of the skin for the patching group and of the lid or conjunctiva for the atropine group) was more common in the patching group than in the atropine group.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Inconsistency, substantial statistical and clinical heterogeneity.
[2]High risk of bias in at least one contributing study.
[3]Imprecision around effect estimates.

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BACKGROUND

Description of the condition

Amblyopia (often referred to as lazy eye) is a common childhood condition and is defined as impaired visual acuity in one or both eyes that is present with no demonstrable abnormality of the visual pathway and is not immediately resolved by wearing glasses. The term is used most frequently to refer to the unilateral condition, although amblyopia may be bilateral. In adults, it is usually diagnosed by a significant reduction in visual acuity that cannot be improved by refractive correction and which has no obvious organic cause (AAO 2012; Ciuffreda 1991; Levi 2006). Factors commonly associated with amblyopia and that are used for classification include strabismus (squint), stimulus deprivation such as cataract or ptosis, and those caused by anisometropia, or unequal refractive error (need for glasses) between the two eyes.

Amblyopia develops during early childhood (infancy to 12 years or older) when the visual system is vulnerable to changes in visual stimulation (Ansons 2001). During this time it is usually a reversible condition. If left untreated it will remain as a permanent visual defect into adulthood (Rahi 2002; Tommila 1981). About 25% of people with amblyopia have a visual acuity in the amblyopic eye worse than 20/100 (Woodruff 1994).

Epidemiology

Amblyopia has the potential to place a substantial burden on patient and healthcare resources, as the visual impairment can last a lifetime. The estimated prevalence of amblyopia is between 2% to 3%, depending on diagnostic criteria used and the population selected (AAO 2012; Attebo 1998; Brown 2000; Flom 1985; PEDSG 2008; PEDSG 2013; Williams 2002). Two Australian adult population-based cohort studies, Visual Impairment Project and Blue Mountains Eye Study, reported the prevalence of unilateral amblyopia as 3.1% and 3.2%, respectively, when amblyopia was defined as best-corrected visual acuity of 6/9 or worse (Attebo 1998; Brown 2000). Lower amblyopia prevalence was reported in preschool screening programs (Williams 2002).

Risk factors associated with the development of amblyopia include premature birth, low birthweight, retinopathy of prematurity, cerebral palsy, intellectual disability, family history of amblyopia, congenital cataract, and maternal factors such as smoking, antihistamine ingestion, and alcohol (AAO 2012; AOA 2004). However, many children who present with amblyopia have none of these risk factors.

Presentation and diagnosis

Amblyopia of certain etiologies may not produce symptoms that are obvious to a parent or the affected child.

Unilateral refractive amblyopia may go unnoticed for years because the child typically has good visual acuity in the normal eye. As a result, many children remain undiagnosed, especially before they begin school. The refractive error is detected at the first examination but a diagnosis of amblyopia cannot be made until the child has been reassessed with refractive correction in place. Bilateral refractive amblyopia can be easier to detect as the child may struggle with close work or complain of reduced or blurred vision.

In strabismic amblyopia, strabismus is present and the eyes are not aligned properly, resulting in one eye being used less than the other. The majority of children with strabismic amblyopia can be detected by the appearance of the strabismus (squint) (AAO 2012). However, the degree of strabismus may range from a very small deviation, for example microtropia (five degrees or less) with useful binocular vision, to a very large deviation, which may affect a person's appearance.

Deprivation amblyopia caused by cataracts may be detected at discharge from hospital of newborns or at eight-week postnatal examination. Cosmetically unacceptable ptosis (droopy lid) will present at an early age for treatment.

The basis of a diagnosis of amblyopia is defective central visual processing, therefore careful assessment of the retina, optic nerve, and all other structures within the eye is essential. Attention should also be paid to the potential risk factors for amblyopia, such as a positive family history for strabismus, amblyopia, or media opacity (AAO 2012). The diagnosis is established by a unilateral or bilateral reduction of best-corrected visual acuity not attributable to structural abnormalities of the visual pathways.

Criteria for a diagnosis of unilateral amblyopia (AAO 2012) include:

1. unequal fixation behavior;
2. 2-octave difference in preferential looking, or ≥ 2 line interocular difference in best-corrected visual acuity.

Description of the intervention

The aim of all treatment options for amblyopia is to obtain the best-possible visual acuity in the amblyopic eye. The initial treatment for any patient with amblyopia is full-time wear of necessary refractive correction. The period of refractive adaptation (time taken to settle into glasses) is thought to be up to 24 weeks (Moseley 2002). A recent Cochrane Review summarized the effectiveness of refractive correction as an initial treatment for amblyopia (Taylor 2012). The initial treatment is usually followed by promoting the use of the amblyopic eye through limiting the use of the sound eye, such as conventional occlusion or atropine penalization. Three published Cochrane Reviews examined various interventions for people with different types of amblyopia (Antonio-Santos 2014; Taylor 2012; Taylor 2014). None of these reviews specifically compared occlusion therapy and atropine penalization, therefore the treatment options addressed within this review were occlusion therapy and atropine penalization.

How the intervention might work

1. Occlusion treatment

Occlusion treatment for amblyopia was first described in 1772 (Fells 1990). Covering the sound eye with an opaque patch forces the patient to use the amblyopic eye. Opinions vary on the number of hours of patching per day that should be prescribed, ranging from one hour to full time (PEDIG 2002), and the concurrent activities while patching is being carried out (PEDIG 2006).

2. Atropine penalization

Atropine penalization has been used as an alternative to occlusion therapy for amblyopia for over a century. Atropine sulphate, a long-acting topical cycloplegic agent, is instilled in the sound eye to blur the vision in the sound eye for near activities (Foley-Nolan

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1997; PEDIG 2002; Swann 1974), hence forcing the amblyopic eye to be used preferentially for near-vision tasks. Atropine penalization can be used alone or in combination with optical penalization (placement of a fogging lens over the sound eye) (Repka 1993). Opinions vary on the number of days that atropine penalization should be prescribed (PEDIG 2004).

Factors affecting outcome

Compliance plays a large role in determining the effectiveness of occlusion therapy (Newsham 2000; Simons 1999; Simons 2005). Prescribed doses of treatment may be less than the actual dose taken by patients. Less treatment may be better tolerated and as effective as a more traditionally used dosage (Wu 2006). In addition, the initial visual acuity, type of amblyopia, treatment initiation age, and the efficacy of the treatment modality may also play a role.

Why it is important to do this review

Occlusion therapy with patching of the sound eye has been the mainstay of amblyopia treatment, however, the success of occlusion depends heavily on compliance. Success rates vary from 30% to 95%, depending on the definition used (e.g. no regress in amblyopic eye, doubling of visual acuity of the amblyopic eye, or an interocular difference of zero) (Kaye 2002; Repka 1993). There are also conceptual concerns about the degree to which unilateral occlusion disrupts binocularity, as well as the number of hours of patching per day that should be prescribed.

The practical benefit of atropine penalization is its ease of administration, reliable assessment of compliance, and low cost. It is believed to be more acceptable than occlusion to both children and their parents because it avoids both the skin irritation and social stigma of a patch (Simons 1997). The reported adherence rates for atropine penalization vary from 78% to 100% (Kaye 2002). The disadvantage of atropine penalization is its potential toxicity and its duration of effect if reverse amblyopia is detected.

Reverse amblyopia, in which the initially better eye is made amblyopic as a result of the treatment, seems particularly likely to arise when patients fail to continue follow-up visits to the treating physician (Simons 1997), which can occur with both treatment options.

A decade has passed since the original version of this systematic review (Li 2009), thus an update was needed to examine both earlier and more recent evidence with regard to the effectiveness and safety of occlusion therapy compared to atropine penalization in treating amblyopia.

OBJECTIVES

In performing this systematic review, we aimed to synthesize the best available evidence regarding the effectiveness and safety of conventional occlusion therapy compared to atropine penalization in treating amblyopia.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs) and quasi-randomized controlled trials (CCTs) in this review. Studies that had not used randomization to allocate participants to treatment groups but had used techniques intended to allocate patients in an unbiased fashion were considered to be quasi-randomized trials. Some examples include allocation based on day of the week, year of birth, or clinic record number of consecutive patients. We imposed no date or language restriction on studies selected for this review.

Types of participants

We included trials that had enrolled participants of any age with either unilateral strabismic, anisometropic, or mixed (strabismic-refractive) amblyopia. Deprivation amblyopia was not included since treatment for this type of amblyopia has been covered in another Cochrane Review (Antonio-Santos 2014). There was no restriction on gender or severity of the amblyopia placed on participants of trials selected for this review.

Types of interventions

We originally planned to include trials that compared conventional occlusion with any pharmacologic therapy, including systemic therapy such as levodopa and carbidopa. Given the comments from the peer reviewers and editors, and the fact that other pharmacological treatments do not penalize the better eye, we decided post hoc to limit this review to trials that compared conventional occlusion (patching) of any type (part time or full time, total adhesive, partial occlusion, optical penalization, shield, and pirate patch) to atropine penalization, with or without conventional occlusion. Systemic pharmacologic treatments for amblyopia were excluded.

Types of outcome measures

Primary outcomes

The primary outcome for this review was mean difference in visual acuity of the amblyopic eye on an age-specific test at 12 months from commencement of treatment analyzed in continuous LogMAR units. The long-term stability of treatment effects is of particular importance to children and parents. For this reason, we chose visual acuity measured after 12 months of treatment as the primary outcome of interest. The primary outcome was also analyzed as dichotomous and categorical data after 12 months of treatment, depending on how data were reported in the trials. The prespecified categories were as follows.

1. Best-corrected visual acuity dichotomized into:
   - normal: 0.2 LogMAR (6/9 or 20/30 Snellen equivalent) or better;
   - residual deficit: worse than 0.2 LogMAR.
2. Change in visual acuity categorized by:
   - 2 or more lines improvement from baseline;
   - no change (within 2 lines of baseline);
   - 2 or more lines loss.

We prespecified that we would analyze visual acuity at other time points when such measurements were reported in the trials.

Secondary outcomes

The secondary outcome for this review was change in binocular function measured by change in stereo acuity according to the stereopsis test applied in each trial. We also considered ocular alignment and adherence to treatment as secondary outcomes. We

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examined the secondary outcome at follow-up times as reported in the included trials.

Quality of life data

We reported any quality of life measures associated with having residual amblyopia and treated amblyopia.

Economic data

We documented the cost of treating amblyopia as reported in the trials.

Harms

We tabulated all systemic and ocular adverse effects related to either conventional occlusion or atropine penalization reported in the included trials. Specific adverse effects of interest were as follows.

Mild

1. Reduction in visual acuity of the sound eye not requiring treatment
2. Allergy to treatment such as skin irritation for patching treatment
3. Mild allergic reaction to atropine not requiring treatment

Severe

1. Reduction in visual acuity of the sound eye requiring further treatment
2. Severe allergy to patches or atropine requiring further treatment
3. Non-resolving double vision due to erosion of suppression
4. Psychological distress

We applied GRADE (Schünemann 2013) to outcomes reported in the included studies and prioritised the following in Summary of findings for the main comparison due to their clinical importance: visual acuity at 6 months, visual acuity at 24 months, adherence to treatment, ocular alignment, stereoacuity, quality of life, and adverse events.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for RCTs and controlled clinical trials. We imposed no language or publication year restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 8) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 7 September 2018) (Appendix 1).
- MEDLINE Ovid (1946 to 7 September 2018) (Appendix 2).
- Embase Ovid (1980 to 7 September 2018) (Appendix 3).
- LILACS BIREME (Latin American and Caribbean Health Science Information Database) (1982 to 7 September 2018) (Appendix 4).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 7 September 2018) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 7 September 2018) (Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 7 September 2018) (Appendix 7).

The first version of this review was published in 2009 (Li 2009). Post-peer review of the original review manuscript we decided to exclude systemic pharmacologic therapy for amblyopia. For this reason, we modified the electronic searches in June 2009 for the review and all future updates of the review.

Searching other resources

We manually searched the reference lists of the reports of trials included in the review for additional trials. We used the Science Citation Index to find studies that had cited the included trials. We searched the Pediatric Eye Disease Investigator Group (PEDIG) website (public.jaeb.org/pedig) for ongoing trials and protocols of included trials. We did not handsearch journals and conference proceedings to find additional trials.

Data collection and analysis

Selection of studies

At least two review authors independently assessed the titles and abstracts identified by the searches against the eligibility criteria. We labeled each abstract as 'include,' 'unclear,' or 'exclude.' We obtained the full-text copies of articles for abstracts labeled 'include' or 'unclear.' Two review authors independently examined each full-text article to determine eligibility for inclusion in the review. Any discrepancies were resolved by discussion between the review authors. We documented the excluded studies and the reasons for their exclusion. For included trials, we obtained all articles pertinent to the trial, abstracted data, and assessed risk of bias. We used Covidence to manage the screening for the update of this review (Covidence 2019).

Data extraction and management

Two review authors independently abstracted data from the included studies onto paper data collection forms developed and pilot-tested specifically for this review. We decided as a priority to extract the following details.

1. Methods: method of allocation, masking of outcome assessment, exclusions after randomization, losses to follow-up, adherence, and other aspects of study design and conduct.
2. Participants: country where participants were enrolled, age, gender, number randomized, main inclusion and exclusion criteria.
3. Interventions: descriptions of the conventional occlusion method and atropine penalization method implemented.
4. Outcomes: primary and secondary outcomes and follow-up periods.
5. Notes: funding sources relevant to each trial.

Any discrepancies were resolved by discussion. One review author entered all data into Review Manager 5 (Review Manager 2014), and a second review author verified the entries.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each trial using the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins

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2017). The following six domains were considered in the 'Risk of bias' assessment: sequence generation; allocation concealment before randomization; masking (blinding) of outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. We did not assess risk of bias due to masking of participants because one cannot mask receipt of patching or eye drops. We assessed each trial for each parameter as having low, high, or unclear risk of bias. We applied GRADE (Schünemann 2013) to the outcomes reported in the included studies and have presented the results in Summary of findings for the main comparison.

Measures of treatment effect

We followed the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* for data analyses (Deeks 2017). We calculated the weighted mean difference for continuous outcomes (e.g. visual acuity, change in stereo acuity). We used risk ratios as the effect measurement for dichotomous outcomes (e.g. visual acuity dichotomized into normal or residual deficit). For trials that reported visual acuity in some notation other than LogMAR, we used a conversion chart via the Keeler LogMAR crowded test.

Unit of analysis issues

In all seven included trials, only one eye from each participant was randomized. The unit of randomization and analysis for efficacy outcomes was the individual eye. If cluster-randomized trials and cross-over trials are included in the future updates of this review, we will extract data from an analysis that properly accounts for the non-independence within the cluster following the guidelines in Section 9.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Dealing with missing data

We analyzed available-case data as reported, which assumes that data are missing at random; we did not impute missing data. We contacted and received responses from the lead investigator for one of the included trials that was missing information (Tejedor 2008).

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of each study qualitatively. We planned to use forest plots of results of the studies, the results of the Chi^2 test for statistical heterogeneity, and the value of the I^2 statistic to estimate the amount of statistical heterogeneity among trials if a meta-analysis were carried out.

Assessment of reporting biases

We planned to use a funnel plot to assess small-study effects when a sufficient number of trials (10 or more) were identified.

Data synthesis

We prespecified that when substantial clinical or statistical heterogeneity was present, we would not combine study results but would present an estimate of effect and associated confidence interval for each individual trial. If there was little variation between trials (I^2 < 60%), we would combine the results in a meta-analysis using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses by the type of amblyopia (strabismic, anisometropic, and mixed amblyopia) and type of occlusion (part-time and full-time occlusion) when sufficient data were available in the included studies.

Sensitivity analysis

We planned to conduct sensitivity analyses to determine the impact of the exclusion of studies of lower methodological quality and industry-funded studies; however, due to the low number of studies eligible for each meta-analysis (three or fewer), we did not conduct sensitivity analyses.

RESULTS

Description of studies

Results of the search

As described previously, the amendment to include only atropine penalization rather than any type of pharmacological therapy in the electronic searches was a post hoc decision. The electronic searches for the first publication of this review retrieved 106 records (26 from CENTRAL, 41 from MEDLINE, and 39 from Embase). After removal of duplicates, we screened 57 titles and abstracts for eligibility, of which 20 records appeared to be relevant. Of the 20 articles that underwent full-text screening, four reports were excluded: three were not reports of RCTs or CCTs, and one did not address the comparisons of interest. The remaining 16 articles describing five trials were relevant to this review; however, at the time the review was published in 2009, only two of these trials had results for inclusion (Foley-Nolan 1997; PEDIG 2002), while three were awaiting classification (Menon 2008; PEDIG 2008; Yan 2008). We identified one additional trial by searching the Science Citation Index (Tejedor 2008). We identified no additional trials by searching the reference lists of included studies or the WHO ICTRP. Altogether, three trials were included in the 2009 version of this review.

In September 2018 we updated the search and identified 192 new records (Figure 1). We removed 85 duplicates and screened the remaining 107 records. We included the three trials previously awaiting classification, Menon 2008; PEDIG 2008; Yan 2008, and one new trial (Medghalchi 2011), as well as four reports of auxiliary studies for trials that had already been included (PEDIG 2002). We excluded five reports of four studies (Huang 2009; Liao 2009; PEDIG 2011; PEDIG 2013). Altogether for this update we included seven studies and excluded eight studies. We did not find any ongoing studies in our search of trial registers.

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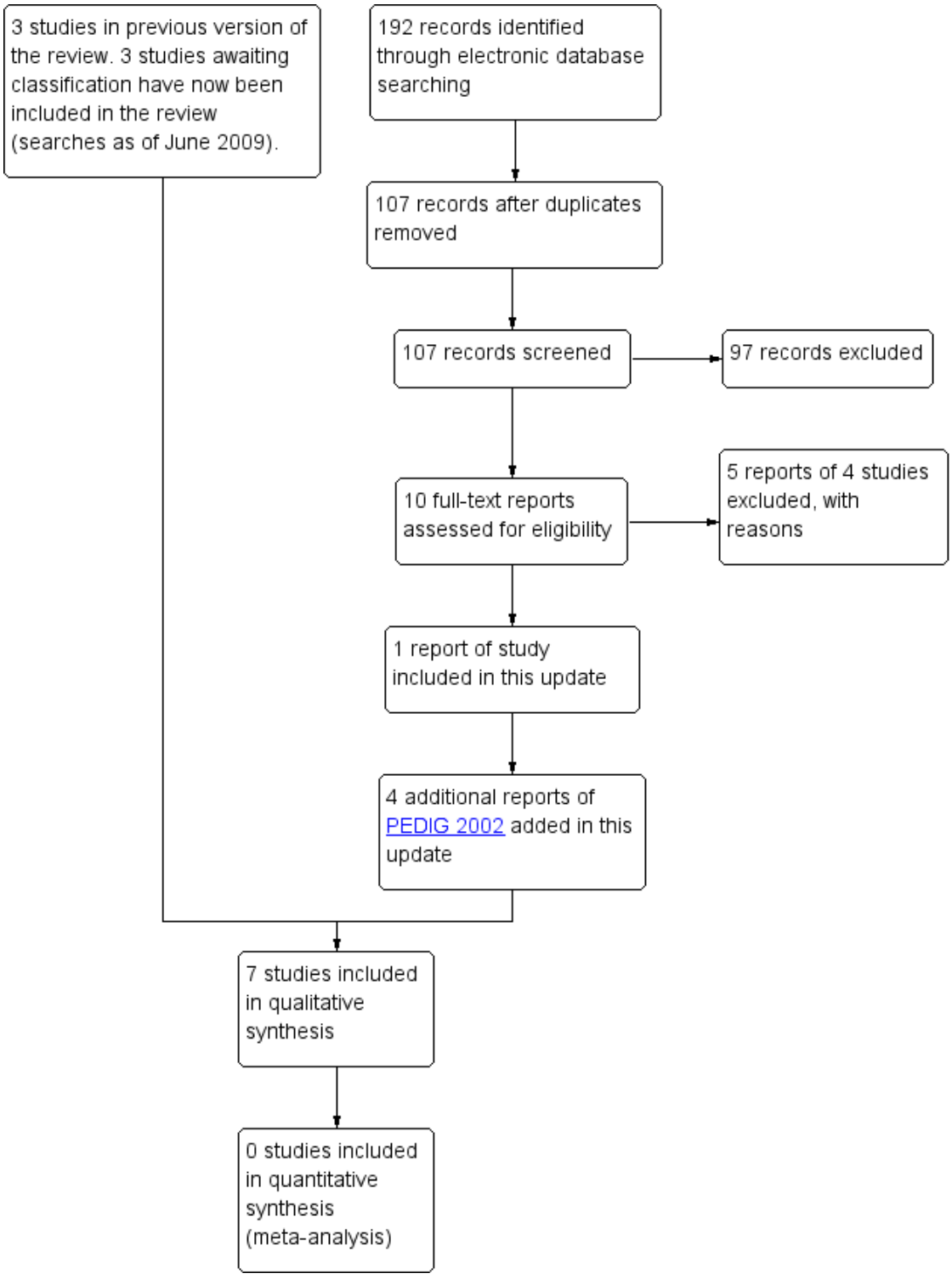
Figure 1. Study flow diagram.



Included studies

For details see Characteristics of included studies.

Participants

We included seven trials in the review from six countries (China, India, Iran, Ireland, Spain, and the United States) with a total of 1177 amblyopic eyes (Foley-Nolan 1997; Medghalchi 2011; Menon 2008; PEDIG 2002; PEDIG 2008; Tejedor 2008; Yan 2008). The trials varied in size, from 36 participants in the smallest trial, Foley-Nolan 1997, to 419 participants in the largest trial (PEDIG 2002). Six trials included boys and girls ages from two to 14 years with varying levels and types of amblyopia (strabismic, anisometric, or both), while the

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seventh trial included participants with anisometropic amblyopia from four to 20 years of age (Menon 2008).

We found clinical heterogeneity in several aspects, including the age of participants, baseline visual acuity, and type of amblyopia. Differential distribution of these factors across trials were of concern because older age at commencement of treatment, worse starting visual acuity, and strabismus as the cause of amblyopia have been related to poorer response to amblyopia treatment (Flynn 1998; Hiscox 1992; Newman 1996; Woodruff 1994).

Foley-Nolan 1997 enrolled 36 children in Ireland younger than nine years of age with all levels and types of amblyopia, although in 92% of participants strabismus was a cause. No participant had received previous treatment prior to their inclusion. Tejedor 2008 enrolled 70 children in Spain between two and 10 years of age. No participant had received previous treatment of amblyopia prior to inclusion. Visual acuity in the amblyopic eye was at least 0.5 LogMAR (i.e. 20/80 Snellen equivalents) (mean = 0.43 LogMAR). The inclusion criteria specified moderate to mild amblyopia. Medghalchi 2011 enrolled 120 children in Iran between four and 10 years of age with visual acuity in the amblyopic eye between 20/40 to 20/100 Snellen equivalent. The levels and types of amblyopia were not reported. Menon 2008 enrolled 63 participants in India between eight and 20 years of age with mild or moderate anisometropic amblyopia and an intereye visual acuity difference of 0.3 LogMAR units. Yan 2008 enrolled 276 children in China between seven and 14 years old with amblyopia. Baseline visual acuity and type of amblyopia were not reported, although children with non-horizontal strabismus were not eligible for the study. The two studies conducted in the United States, PEDIG 2002 and PEDIG 2008, enrolled 419 children younger than seven years of age with all types of amblyopia and 193 children between seven and 13 years of age with all types of amblyopia, respectively. Baseline vision in the amblyopic eye ranged from 0.3 to 0.7 LogMAR (20/40 to 20/100 Snellen equivalent) in both of these studies. Children in whom any ocular pathology was present or who had received more than two months of amblyopia therapy in the past two years were excluded from the PEDIG 2002 study. Foley-Nolan 1997 included amblyopic eyes of worse baseline visual acuity and a larger proportion of children with strabismic amblyopia compared with the other trials. Menon 2008, which was conducted in India, included older amblyopic participants compared with the other trials and only involved participants with anisometropic amblyopia.

Interventions

The included trials evaluated a range of interventions and prescribing regimens. Different regimens of occlusion, including partial occlusion in Tejedor 2008 and total occlusion in the remaining six trials, and atropine penalization were compared. Duration of occlusion ranged from two hours per day to full time for periods from 17 weeks to two years. Specifically, Foley-Nolan 1997 prescribed full-time total occlusion for one week per year of life. Once vision improved to 6/9 or better, occlusion was reduced to half days. The average duration of full-time total occlusion was 4.3 months (range two to nine months), but adherence was documented as only 55%. Menon 2008 also prescribed full-time occlusion, but alternated occlusion of the sound eye and amblyopic eye on a 6:1 day ratio for six months. In Yan 2008, total occlusion was prescribed for six hours per day until visual acuity of 0.9 LogMAR was reached or when visual acuity remained static for three months. PEDIG 2002 prescribed a minimum of six hours daily occlusion with some participants (20%) prescribed 12 hours daily over the initial six-month period. After six months, atropine or patching was followed by best clinical care for two years. The variable nature of the occlusion regimens for the participants makes it difficult to report exactly how much occlusion was worn by the participants. Excellent adherence was documented in 49% of cases. In the shortest study, PEDIG 2008, total occlusion was prescribed for 17 weeks beginning at two hours each day, with near vision work to be done during one hour of occlusion. If after five weeks vision had not improved at least 5 letters from baseline, occlusion was increased to four hours per day. If at five weeks visual acuity was 79 letters or better, occlusion treatment was continued or decreased to one hour per day. Occlusion regimens in Medghalchi 2011 were determined by baseline differences in vision between eyes. Children with 2 Snellen lines or less difference were prescribed two hours per day, and those with 3 Snellen lines or more were prescribed three hours per day. The treatment period was two years. Tejedor 2008 used partial occlusion by means of positive defocus of the sound eye over a treatment period of six months.

The comparison intervention, atropine penalization, was also prescribed variously among the seven trials. Foley-Nolan 1997, Menon 2008, PEDIG 2002, and Yan 2008 initially prescribed one drop per day of atropine sulphate 1%. Treatment was discontinued or tapered when visual acuity goals, as defined by individual studies, were met. The frequency of administration was increased to twice daily in the Menon 2008 study when no improvement in visual acuity was observed. Tejedor 2008 prescribed 1% atropine twice weekly when interocular acuity difference was present, and once weekly for maintenance therapy. Medghalchi 2011 prescribed atropine 0.5% twice weekly. The dose was decreased to once weekly when visual acuity improved. PEDIG 2008 prescribed atropine 1% on a weekend basis (Saturdays and Sundays) in addition to one hour of near work per day for 17 weeks. Whenever no improvement in visual acuity was observed after five weeks, treatment frequency was increased to daily instillation. Weekend atropine provided a similar improvement in vision to daily atropine for participants aged between three and seven years with moderate amblyopia (0.3 to 0.6 LogMAR, 20/40 to 20/80 Snellen equivalent) (PEDIG 2004).

Outcomes

All trials assessed visual acuity in the amblyopic eye, while four trials also assessed visual acuity in the sound eye (Foley-Nolan 1997; PEDIG 2002; PEDIG 2008; Tejedor 2008). However, the vision tests used varied among studies: PEDIG 2002 used the validated Amblyopia Treatment Study visual acuity testing protocol; PEDIG 2008 used the E-ETDRS visual acuity testing protocol; Menon 2008 used Snellen and ETDRS charts; Tejedor 2008 used the LogMAR Crowded Glasgow acuity cards; Foley-Nolan 1997 used the Snellen chart, Kay's Pictures, or Sheridan-Gardiner opto types, depending on the age and comprehension of the patient; and Medghalchi 2011 used an E chart (nidek projector). Specific vision tests were not reported in Yan 2008, although visual acuities were reported as LogMAR values. Different measurement instruments may introduce information bias and heterogeneity in determining visual acuity outcomes. Certain vision tests are known to be comparable, such as crowded Kay's Pictures and Crowded LogMAR, although crowded Kay's Pictures is an easier test for children to perform (Jones 2003).

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The time point at which visual acuity was recorded during the trial also varied considerably, with study durations ranging from 17 weeks, PEDIG 2008, to 24 months, Medghalchi 2011; PEDIG 2002. None of the included trials examined visual acuity at 12 months, the time point specified for the primary outcome of this review. In the shortest study (PEDIG 2008), visual acuity was measured at baseline, five weeks, and 17 weeks. Visual acuity was measured at baseline and at monthly intervals for six months in Menon 2008. The follow-up schedule for Tejedor 2008 was appointments every two to six months, depending on the severity of amblyopia and the response to treatment; however, for statistical analysis data were recorded at three- and six-month follow-up examinations. PEDIG 2002 investigators assessed visual acuity at baseline and six and 24 months follow-up. In Medghalchi 2011, measurements were taken at baseline and 24 months. Two studies had indiscriminate timescales for follow-up: Foley-Nolan 1997 at baseline, the conclusion of therapy (treatment was considered to have been concluded when a visual acuity of 6/6 was achieved, or when visual acuity remained static over three successive assessments), and after the longest-term follow-up, and Yan 2008 at the conclusion of therapy (treatment was considered to have been concluded when a LogMAR visual acuity of 0.9 was achieved, or when visual acuity remained static for three months). Different follow-up schedules may introduce heterogeneity that affects the outcome, as the effects of treatment may vary with time.

Five trials examined stereo acuity outcomes using various measurement tools, such as the TNO stereo test, Titmus fly test, Randot preschool stereo acuity test, and Randot circles stereo acuity test (Medghalchi 2011; Menon 2008; PEDIG 2002; PEDIG 2008; Tejedor 2008). Ocular alignment was evaluated in three trials (PEDIG 2002; PEDIG 2008; Yan 2008).

Safety and adherence to treatments were also reported.

Excluded studies

We excluded eight studies of those articles for which we reviewed the full texts (Chatzistefanou 2000; Cole 2001; Huang 2009; Liao 2009; PEDIG 2011; PEDIG 2013; Scheiman 2005; Wu 2006): three were not reports of RCTs or CCTs, and five did not address the comparisons of interest for this review. The clinical characteristics for each excluded study are shown in the Characteristics of excluded studies table.

Risk of bias in included studies

We evaluated the risk of bias for each trial using six prespecified criteria. We assessed PEDIG 2002 and PEDIG 2008 as having the lowest risk of bias and Foley-Nolan 1997 and Medghalchi 2011 as having the highest risk of bias among the seven included trials. We also interpreted the possible effect of methodological differences among studies; investigated the strength and weakness of the evidence; and determined whether studies should be combined in a meta-analysis (see Figure 2 'Methodological quality summary').

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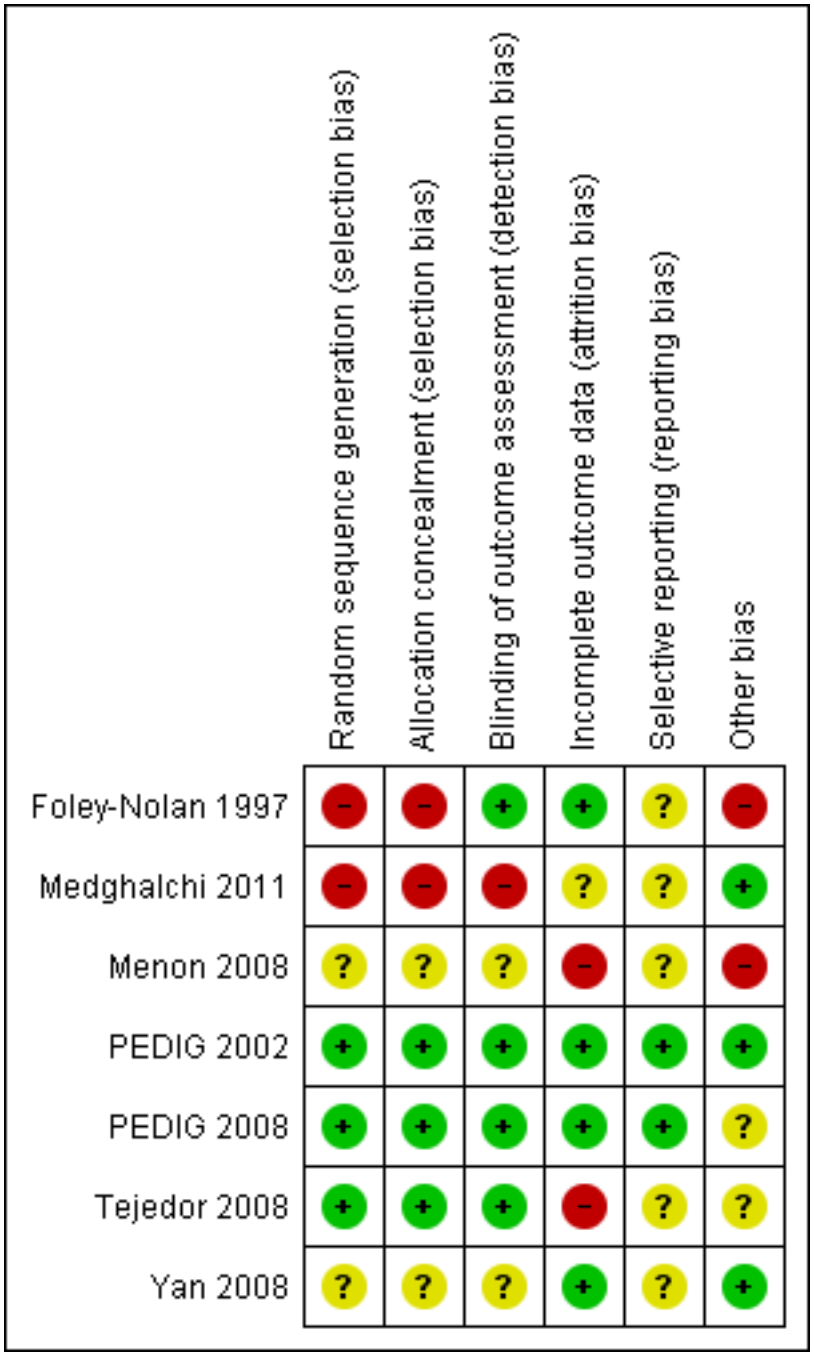
Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Sequence generation

The randomization sequence was inadequately generated in two studies. Participants were assigned to treatment groups on an alternate basis in Foley-Nolan 1997 and by even versus odd medical record numbers in Medghalchi 2011. Because patient assignment involved such a systematic or non-random approach, confounding may have been introduced. PEDIG 2002, PEDIG 2008, and Tejedor 2008 used computer-generated random numbers, which we deemed an appropriate sequence generation method. The method of randomization was not reported in two studies (Menon 2008; Yan 2008).

Allocation concealment

Adequate allocation concealment before randomization further prevents selection bias. We considered that investigators who enrolled participants could possibly have foreseen assignment in Foley-Nolan 1997 and Medghalchi 2011, and thus may have introduced selection bias. Randomization in PEDIG 2002 and PEDIG 2008 was accomplished on the studies' websites, which is one form of central allocation with adequate concealment. Tejedor

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2008 did not report in the article how allocation was concealed; through written personal communication, the lead investigator informed us that a central office steering committee handled the randomization process so that investigators who determined eligibility and enrolled individuals were unaware of the assignment order. Allocation concealment was not reported in two trials (Menon 2008; Yan 2008).

Masking of outcome assessors (detection bias)

The primary outcome for this review was visual acuity in the amblyopic eye. Four trials masked personnel who assessed visual acuity. Specifically, PEDIG 2002 reported that the vision tester was masked to treatment group for 97% of the examinations at six months, and 92% at 24 months. Examiners in PEDIG 2008 were masked to treatment groups by having the sound eye patched for all participants at the 17-week visit. The reported success of masking in Tejedor 2008 was 90.6% (29/32) of the optical and 87% (27/31) of the pharmacologic penalization groups. Visual acuity examiners were reported as masked in Foley-Nolan 1997. No masking was done in Medghalchi 2011. Whether or not masking was implemented in Menon 2008 or Yan 2008 was not reported.

Incomplete outcome data

Menon 2008 excluded six (10%) participants, and Tejedor 2008 excluded seven (10%) participants from the analyses. Excluding randomized participants from analyses was of particular concern because those excluded may have had a different distribution of prognostic factors and different responses to treatment from those retained, and therefore may introduce bias. Post-treatment visual acuity was reported for all 36 participants in Foley-Nolan 1997 and all 276 participants in Yan 2008. PEDIG 2002 had 96% and 95% follow-up rates at six months and two years, respectively. PEDIG 2008 had 89% follow-up at 17 weeks. All analyses in the two PEDIG studies followed the intention-to-treat principle with missing values handled using last follow-up value carried forward method. Medghalchi 2011 reported and analyzed only participants with two years of follow-up data; it was unclear whether more participants were enrolled in the study but excluded due to missing data.

Selective reporting

We had insufficient information to assess the risk of selective reporting bias in five studies (Foley-Nolan 1997; Medghalchi 2011; Menon 2008; Tejedor 2008; Yan 2008). All outcomes listed in the PEDIG baseline papers and protocols were reported in the subsequent publications (PEDIG 2002; PEDIG 2008).

We did not assess the potential for publication bias using a funnel plot because only seven trials were included.

Other potential sources of bias

The statistical analyses for four trials were inadequate (Foley-Nolan 1997; Medghalchi 2011; Menon 2008; Tejedor 2008). The analyses compared pre- and post-treatment visual acuity of participants in each treatment group. However, no between-group comparison was made and therefore no meaningful inference could be drawn. Tejedor 2008 and Menon 2008 provided standard deviations for the visual acuity improvement in each arm. We used this information to calculate the between-group effect estimates. However, these estimates should be interpreted cautiously because missing values have not been accounted for.

The 'Risk of bias' assessment alerted us to three studies with methodological concerns (Foley-Nolan 1997; Medghalchi 2011; Menon 2008). The study characteristics, including study methods, population, and intervention, varied across trials. As a result of substantial clinical heterogeneity, we decided not to pool the quantitative data in a meta-analysis. Instead, we reported the results separately for each trial wherever data were available.

Effects of interventions

See: **Summary of findings for the main comparison** Conventional occlusion compared to atropine penalization for amblyopia

Visual acuity outcomes

Of the seven included trials, data were available for the comparison of conventional occlusion versus atropine penalization for at least one visual acuity outcome. There was heterogeneity among the studies in the study population as well as the reporting of outcomes and the time points at which outcomes were measured (Table 1). We therefore did not perform any meta-analysis due to the clinical, methodological, and statistical heterogeneity.

At 5 weeks follow-up (1 trial; 180 participants)

In PEDIG 2008, the mean visual acuity at 5 weeks follow-up for participants in the conventional occlusion group (91 participants) was less than 1 letter better than participants in the atropine penalization group (89 participants) (mean difference (MD) 0.01 LogMAR, 95% confidence interval (CI) −0.02 to 0.05) after adjusting for visual acuity at baseline (Analysis 1.1). Both groups improved more than 1 line of visual acuity from baseline (6.8 letters in the conventional occlusion group and 6.2 letters in the atropine group).

At 17 weeks follow-up (1 trial; 180 participants)

In PEDIG 2008, the mean visual acuity for participants in the conventional occlusion group (91 participants) was less than 1 letter better than participants in the atropine penalization group (89 participants) (MD 0.02 LogMAR, 95% CI −0.01 to 0.06) at 17 weeks follow-up after adjusting for visual acuity at baseline (Analysis 1.1).

At 6 months follow-up (3 trials; 552 participants)

Three trials reported mean visual acuity at six months of follow-up (Menon 2008; PEDIG 2002; Tejedor 2008). Two of the three trials reported statistically significant differences between the atropine penalization and conventional occlusion groups at six months (PEDIG 2002; Tejedor 2008). These differences were small, and both groups experienced similar improvement from baseline visual acuity.

In PEDIG 2002, visual acuity in the amblyopic eye improved substantially from baseline to six months in both the patching and atropine group (3.16 lines and 2.84 lines, respectively). Improvement was initially faster in the patching group, but at six months the difference in visual acuity between the two treatment groups was small and clinically inconsequential (MD 0.034 LogMAR, 95% CI 0.005 to 0.064 LogMAR) (Analysis 1.1). The six-month visual acuity was 0.2 LogMAR (6/9 or 20/30 Snellen equivalent) or better in the amblyopic eye in 63.5% (132/208) of the patching group and 53.1% (103/194) of the atropine group (risk ratio (RR) 1.20, 95% CI 1.01 to 1.41) (Analysis 1.2). Among participants who had both baseline and six-month visual acuity measurement, 87.0% (181/208) of the patching group and 82.5% (160/194) of the atropine

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group gained 2 or more lines of vision in the amblyopic eye from baseline (RR 1.06, 95% CI 0.97 to 1.15) (Analysis 1.3); 13.0% (27/208) of the patching group and 17.5% (34/194) of the atropine group had visual acuity within 2 lines of baseline (RR 0.74, 95% CI 0.46 to 1.18) (Analysis 1.4); and no participant experienced a loss of 2 or more lines of vision in either the patching or atropine group.

In Tejedor 2008, improvement in visual acuity from baseline occurred in both the optical penalization and atropine group. The trial authors did not report the effect estimates (e.g. mean difference, risk ratio) between groups. We calculated the effect estimates and CIs based on available information. Visual acuity in the amblyopic eye improved by 1.8 lines in the optical penalization group and 3.4 lines in the atropine penalization group, and the mean final visual acuity in the atropine and optical penalization groups were 0.07 and 0.21, respectively (MD −0.14 LogMAR, 95% CI −0.23 to −0.05 LogMAR) (Analysis 1.1). Improvement in vision was greater in the atropine group than in the optical penalization group. Visual acuity was 0.2 LogMAR or better (6/9 or 20/30 Snellen equivalent) in the amblyopic eye in 56.3% (18/32) of the optical penalization group and 74.2% (23/31) of the atropine group (RR 0.76, 95% CI 0.52 to 1.10) (Analysis 1.2). At six months, 56.3% (18/32) of children treated with optical penalization and 87.1% (27/31) of those treated with atropine gained 2 or more lines of vision in the amblyopic eye from baseline (RR 0.65, 95% CI 0.46 to 0.90) (Analysis 1.3); 43.8% (14/32) of the patching group and 12.9% (4/31) of the atropine group had visual acuity within 2 lines of baseline (RR 3.39, 95% CI 1.25 to 9.17) (Analysis 1.4); and no participant experienced a loss of visual acuity in the amblyopic eye.

In Menon 2008, visual acuity was reportedly significantly improved from baseline to six months and was the same between the atropine and patching groups at baseline and each follow-up visit, suggesting no difference in response to treatment. The trial authors reported P values for effect estimate (e.g. mean difference) between groups, but did not report the estimate itself. We calculated the effect estimate and CI based on available information. Visual acuity improved by 2.38 lines in the patching group and 2.34 lines in the atropine group (MD −0.02 logMAR, 95% CI −0.11 to 0.07 logMAR) (Analysis 1.1). Although data were available for our primary outcome in this trial, we could draw limited inference regarding the effectiveness of patching versus atropine for two reasons. First, trial authors excluded six participants (three from each group) from the trial analysis due to incomplete follow-up after their second visit. Second, the trial had a very low power to detect any effect on visual acuity — reported by trial authors to be 6%.

We judged the evidence for mean visual acuity at six months to be of moderate certainty, due primarily to substantial statistical and clinical heterogeneity in trial populations.

At less than 12 months follow-up (1 trial; 36 participants)

In Foley-Nolan 1997, participants were randomized to either full-time patching for one week per year of life or 1% atropine sulphate drops instilled daily. Consequently, the treatment interval ranged from two to nine months (mean 4.3 months) for the occlusion group and one to 12 months (mean 7.2 months) for the atropine group. The primary outcome for the trial was change in visual acuity of the amblyopic eye at the end of treatment. The analyses compared pre- and post-treatment visual acuity in each treatment group; no between-group comparison was made. Visual acuity in the amblyopic eye improved from baseline to a mean of 0.66 LogMAR units in the patching group and 0.5 LogMAR in the atropine group. Visual acuity was 0.2 LogMAR or better (6/9 or 20/30 Snellen equivalent) in the amblyopic eye in 44.4% (8/18) of the occlusion group and 61.1% (11/18) of the atropine group (RR 0.73, 95% CI 0.39 to 1.37). Although individual patient outcome data were available, we could not justify calculating the MD and the 95% CI for two reasons. First, three different vision charts were used to measure visual acuity (see Types of outcome measures). Second, we were concerned that the visual acuity was measured at different time points for each child. We could draw limited inference from this trial regarding the relative effectiveness of patching versus atropine on visual acuity.

At 24 months follow-up (2 trials; 483 participants)

Two trials reported visual acuity at 24 months of follow-up (Medghalchi 2011; PEDIG 2002). Neither trial specified visual acuity at 24 months as their primary outcome. Neither trial found any difference between the atropine penalization or patching groups; both groups experienced similar improvement in visual acuity by 24 months.

In PEDIG 2002, additional visual acuity improvement in the amblyopic eye was seen in both treatment groups. Visual acuity improved from baseline to 24 months by a mean of 3.7 lines in the patching group and 3.6 lines in the atropine group. There continued to be no meaningful difference between groups in mean visual acuity score (MD 0.01 LogMAR, 95% CI −0.02 to 0.04 LogMAR) (Analysis 1.1). The 24-month acuity was 0.2 LogMAR (6/9 or 20/30 Snellen equivalent) or better in the amblyopic eye in 75.0% (141/188) of the patching group and 70.9% (124/175) of the atropine group (RR 1.06, 95% CI 0.93 to 1.20) (Analysis 1.2). Among participants who had both baseline and 24-month visual acuity measurements, 90.4% (170/188) of the patching group and 86.9% (152/175) of the atropine group gained 2 or more lines of vision in the amblyopic eye from baseline (RR 1.04, 95% CI 0.97 to 1.12) (Analysis 1.3); 9.6% (18/188) of the patching group and 12.6% (22/175) of the atropine group had visual acuity within 2 lines of baseline (RR 0.76, 95% CI 0.42 to 1.37) (Analysis 1.4); and one participant in the atropine group experienced a loss of 2 or more lines of vision in the amblyopic eye.

In Medghalchi 2011, there was an improvement from baseline to 24 months in both the occlusion and atropine penalization group. The trial authors did not report the specific numbers of participants experiencing outcomes, the standard deviations for the estimated visual acuity, or the between-group effect estimates. The proportion of participants with 2 or more lines of improvement in visual acuity or a visual acuity of 20/30 or better was 76% in the occlusion group and 74% in the atropine group (Analysis 1.3). The mean LogMAR in the occlusion group was 0.15, whereas it was 0.17 in the atropine penalization group. The trial authors reported no significant difference between the two groups in mean visual acuity or lines of improvement. Due to the lack of precision measures, however, we could not calculate the effect estimates and confidence intervals. Additionally, incomplete reporting and predictable treatment allocation introduced the potential for selection bias and reporting bias. For these reasons, we could draw only limited inference from this trial for the effect of occlusion versus atropine on visual acuity.

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We judged the evidence for mean visual acuity at 24 months to be of moderate certainty because one of the contributing studies had a low risk of bias and the other a high risk of bias.

Long-term follow-up (1 trial; 188 participants)

Reports have also been published describing the long-term outcomes of the PEDIG 2002 trial, assessed when participants were 10 and 15 years of age. Of the 419 participants younger than 7 years of age who were originally enrolled, 188 consented to participation in an extended period of follow-up. Of the 188 children in the extension cohort, 176 (94%) were examined at 10 years of age and 152 (80.9%) were examined at 15 years of age. There was no meaningful difference in LogMAR visual acuity between the patching and atropine groups at 10 years of age (MD 0.03, 95% CI −0.02 to 0.08) or at 15 years of age (MD 0.01, 95% CI −0.04 to 0.06).

Subgroup analyses

Three trials assessed the modifying effects of baseline patient characteristics on the treatment group differences in amblyopic eye acuity (Menon 2008; PEDIG 2002; Tejedor 2008).

PEDIG 2002 found that at six months a beneficial effect of both patching and atropine was present in all subgroups based on patient characteristics. The relative treatment effect did not vary with age (P = 0.84), cause of amblyopia (P = 0.68), or baseline amblyopic eye visual acuity (P = 0.59). Participants with visual acuity of 20/80 to 20/100 appeared to improve faster when a greater number of hours of patching was prescribed, but by six months, the amount of improvement was not associated with the number of hours of patching that had been initially prescribed.

Menon 2008 performed a subgroup analysis based on the severity of baseline amblyopia and found the effect was present in all subgroups and similarly to the overall effect, did not differ by treatment status within subgroups. Among those with moderate amblyopia at baseline, the mean visual acuity in the patching group did not differ from the atropine group (MD −0.06 LogMAR, 95% CI −0.03 to 0.15 LogMAR), nor was there any difference among those with mild amblyopia at baseline (MD 0.09 LogMAR, 95% CI −0.22 to 0.04 LogMAR).

Tejedor 2008 carried out subgroup analysis to assess the effect of the type of amblyopia and the age of the participant on treatment outcomes. Subgroup analysis showed that atropine had a greater response in both strabismic and anisometropic amblyopia compared to optical penalization (P = 0.02 strabismic amblyopia; P = 0.02 anisometropic amblyopia). The response to treatment after six months was better but not significantly different in children younger than eight years compared to those eight years and over in the atropine group (P = 0.07) and the optical group (P = 0.09).

Secondary outcomes

Stereo acuity (5 trials; 865 participants)

Five trials examined stereo acuity outcomes using various measurement tools, such as the TNO stereo test, Titmus fly test, Randot preschool stereo acuity test, and Randot circles stereo acuity test (Medghalchi 2011; Menon 2008; PEDIG 2002; PEDIG 2008; Tejedor 2008).

Stereo acuity was examined at 17 weeks in PEDIG 2008; two years in PEDIG 2002 and Medghalchi 2011; six months in Menon 2008; and cessation of treatment in Tejedor 2008. None of the trials reported a statistically significant difference in stereo acuity achieved between groups. PEDIG 2002 and PEDIG 2008 reported no difference between treatment groups in stereopsis. Medghalchi 2011 reported no difference in stereo acuity, with about 35% of participants in the patching group achieving stereo acuity of 400 seconds of arc by the end of follow-up as compared to 30% of participants in the atropine group. Menon 2008 quantified stereo acuity using a TNO test and reported a mean of 747 seconds of arc in the patching group and 677 in the atropine group (MD −69.70 seconds of arc, 95% CI −250.15 to 110.75 seconds of arc). Tejedor 2008 reported a mean stereo acuity measure on the Randot preschool stereo acuity test of 447 seconds of arc in the optical penalization group and 403 in the atropine group at six months (MD 44.28 seconds of arc, 95% CI −100.28 to 188.84 seconds of arc).

We judged the evidence for stereo acuity to be of moderate certainty due to at least one of the contributing studies having a high risk of bias.

Ocular alignment (3 trials; 888 participants)

Three trials studied ocular alignment (PEDIG 2002; PEDIG 2008; Yan 2008).

PEDIG 2002 and PEDIG 2008 reported no evidence of a difference in the number of participants in each treatment group who developed strabismus or showed changes in pre-existing strabismus. Yan 2008 reported that 18/135 (13%) participants in the patching group had an increase of strabismus degree 8△ or more compared with 24/141 (17%) in the atropine group (RR 0.78, 95% CI 0.45 to 1.38). In terms of decreased strabismus, 24/135 (18%) participants in the patching group had a decrease of strabismus degree 8△ or more compared with 33/141 (23%) in the atropine group (RR 0.76, 95% CI 0.47 to 1.22).

We judged the evidence for ocular alignment to be of moderate certainty due to wide confidence intervals around the individual trial estimates.

Adherence to treatment (4 trials; 588 participants)

Four trials reported adherence to treatment (Foley-Nolan 1997; Menon 2008; PEDIG 2002; Tejedor 2008). Due to significant statistical heterogeneity (I^2 = 81%) and differences between the study populations and methods for assessing adherence, we did not perform a meta-analysis of adherence (Analysis 1.5).

As part of PEDIG 2002, the Amblyopia Treatment Index questionnaire was developed to assess the psychosocial impact on the child and family of patching and atropine. The Amblyopia Treatment Index questionnaire asked questions on one of three underlying factors: adverse effects of treatment, difficulties with adherence, and social stigma of the treatment. The internal-consistency reliability for the overall scale was 0.89. The results indicated that both atropine and patching treatments were well tolerated by the child and family, although atropine received more favorable scores overall and on all three questionnaire subscales. The scores of the patching group were better than might have been anticipated based on the investigators' clinical experience. Patient adherence — an average score across follow-up as assessed by investigators according to the percentage of prescribed treatment that was completed at each study visit (excellent, 76% to 100%; good, 51% to 75%; fair, 26% to 50%; and poor, 25% or less) — to the

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occlusion protocol was documented as excellent in 49% (102/208) of cases compared to 78% (151/194) of cases in the atropine group (RR 0.63, 95% CI 0.54 to 0.74).

Tejedor 2008 assessed adherence to atropine penalization by dynamic retinoscopy, and in the optical penalization group "peeking over top of glasses" was documented by examiners during assessments. The number believed to be adherent was 27/32 (84.4%) of the optical penalization group compared with 27/31 (87.1%) of the atropine group (RR 0.97, 95% CI 0.79 to 1.18).

Foley-Nolan 1997 reported that adherence — rated by parents as good (treatment used all of time), average (treatment used two-thirds of time), or poor (treatment used less than a third of time) — was "good" for only 55% (10/18) in the patching group compared to 94% (17/18) in the atropine group (RR 0.59, 95% CI 0.38 to 0.90).

Menon 2008 graded adherence of participants as "good" (patching not missed on any day of one-month follow-up) and "average" (patching not done for one day or more in a month). The trial authors reported no difference in adherence between groups with 18/29 (62%) participants in the patching group and 16/28 (57%) participants in the atropine group having average adherence with treatment (RR 1.09, 95% CI 0.71 to 1.67).

We judged the evidence for treatment adherence to be of moderate certainty due to high risk of bias in at least one of the contributing studies and variations in definitions and methods of assessment.

Psychosocial impact and quality of life (2 trials; 256 participants)

Two trials reported outcomes related to quality of life (Menon 2008, PEDIG 2008).

The authors of Menon 2008 reported that "most patients and parents appeared to prefer atropine penalization over patching" due to cosmetic and psychological reasons; however, the difference between groups was not statistically significant. In PEDIG 2008, investigators administered Amblyopia Treatment Index questionnaires to parents of participants. Although scores were comparable between patching and atropine groups for the adverse events subscale (means of 2.27 versus 2.32 at 5 weeks, P = 0.72; and means of 2.28 versus 2.22 at 17 weeks, P = 0.70), parents scored social stigma (means of 2.21 versus 1.91 at 5 weeks, P = 0.03; and means of 2.37 versus 1.91 at 17 weeks, P < 0.001) and adherence (means of 2.46 versus 2.03 at 5 weeks, P = 0.001; and means of 2.59 versus 2.03 at 17 weeks, P < 0.001) subscales higher for treatment with patching than atropine, favoring atropine. However, these data should be interpreted with caution as 41/193 (21%) of questionnaires were not completed by parents at the five-week visit and 60/193 (31%) were not completed at the 17-week visit.

We judged the evidence for quality of life to be of moderate certainty due to one of the two trials having a high risk of bias.

Economic data

The cost of the atropine regimen is less than that of the patching regimen. PEDIG 2002 estimated the cost for six months of daily patching to be about USD 100 and that for atropine to be about USD 10. This did not include physician visit cost.

Harms

Mild reduction in the visual acuity of the sound eye and light sensitivity (2 trials; 612 participants)

Visual acuity in the sound eye was the primary safety outcome of concern. PEDIG 2002 reported that at six months, visual acuity in the sound eye was decreased from baseline by 1 line in 14 participants in the patching group and 30 participants in the atropine group, and by 2 or more lines in three participants and 17 participants, respectively. Altogether, 17 participants experienced mild visual acuity reduction of the sound eye that did not require treatment in the patching group compared to 47 in the atropine group (see Table 2 'Harms of treatments at 6 months follow-up in PEDIG 2002'). Only one child in the atropine group was actively treated for reduction in visual acuity in the initially sound eye. Many cases of decreased sound eye acuity in the atropine group appeared to be associated with improper refractive correction combined with a residual cycloplegic effect of the atropine (PEDIG 2002). This was supported by subsequent follow-up examinations in which 40 out of 45 participants had a same or a better visual acuity than that at baseline. PEDIG 2002 also reported light sensitivity in 35 (18%) participants receiving atropine and none receiving patching.

PEDIG 2008 reported no difference between treatment groups in the number of participants who had an increase or decrease in a pre-existing strabismus or who developed new-onset strabismus over the 17 weeks of follow-up. The most common adverse event in the atropine group was light sensitivity (14/95), and this was not reported in the patching group (see Table 3 'Harms of treatments at 17 weeks follow-up in PEDIG 2008').

We judged the evidence for mild reduction in visual acuity of the sound eye and light sensitivity to be of high certainty.

Other adverse events

PEDIG 2002 also reported mild and severe skin irritation of patching treatment in 85 (41%) and 13 (6%) participants, respectively. In the atropine group, lid or conjunctival irritation was reported in 8 (4%) participants, and eye pain or headache in 4 (2%) participants. One case in each group developed strabismus and ocular deviation of more than 8△.

PEDIG 2008 reported moderate to severe irritation in 4% (4/98) of participants in the patching group, but none in the atropine group. Additionally, one case each of tachycardia, dry mouth, irritability, and headache were reported in the atropine group, but none in the patching group.

Tejedor 2008 reported one case of reverse amblyopia for the atropine group. Treatment was discontinued, and at subsequent examination the problem resolved without further intervention.

Foley-Nolan 1997 found no refractive change in the sound eye of any study participant; none of the 18 participants using atropine developed irritation of eyelids.

Menon 2008 reported itching and redness and found no difference between groups in the development of itching around the eyes (8/29 in the patching group and 5/28 in the atropine group), but that more participants in the atropine group developed redness in the eye (2/29 in the patching group and 8/28 in the atropine group).

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Medghalchi 2011 and Yan 2008 did not report any adverse events.

DISCUSSION

Amblyopia is the most common cause of monocular visual impairment in both children and young to middle-aged adults (Attebo 1998; Simons 1996). Occlusion therapy with patching of the sound eye has been the mainstay of amblyopia treatment, although the success of occlusion depends heavily on adherence. Occlusion therapy has been prescribed in varying regimens, ranging from a few hours a day to full-time patching, from partial occlusion to total occlusion, as a stand-alone therapy, or in conjunction with another therapy. Atropine penalization has been studied in clinical trial settings as an alternative to occlusion therapy for amblyopia. This method involves instillation of atropine sulphate eyedrops into the sound eye to prevent accommodation and therefore induces blurred vision for near fixation. The accompanying dilation of the pupil also enhances this image degradation. The practical benefit of atropine penalization is its ease of administration, reliable assessment of adherence, and relative low cost. In this systematic review we aimed to identify and synthesize the available RCT evidence with regard to effectiveness and safety of patching compared to atropine therapy in treating amblyopia.

Summary of main results

Evidence from six of the seven included trials suggests that both conventional occlusion and atropine penalization produce visual acuity improvement in the amblyopic eye (Foley-Nolan 1997; Medghalchi 2011; Menon 2008; PEDIG 2002; PEDIG 2008; Tejedor 2008). Atropine penalization appears to be as effective as conventional occlusion in improving visual acuity in the amblyopic eye, although the magnitude of improvement differed among the trials. With regard to binocular function, there is no evidence of a difference between patching and atropine penalization in ocular alignment and stereo acuity. Both treatments were well tolerated. Atropine was associated with better adherence, better quality of life (as reported by parents), but higher reported rates of adverse events in terms of mild reduction in the visual acuity of the sound eye not requiring treatment and light sensitivity. Lastly, the cost of the atropine regimen is likely less than that of the patching regimen.

Overall completeness and applicability of evidence

This review included seven trials with a total of 1177 amblyopic eyes and involved participants ranging in age from 2 to 20 years. All types (excluding stimulus deprivation) and levels of amblyopia were included. Evidence from these trials suggests that atropine penalization results in a similar improvement in visual acuity of the amblyopic eye compared to conventional occlusion for moderate amblyopia. As adverse events were also comparable, it appears reasonable for the physician to offer both treatments impartially and allow for patient/parental choice in the treatment decision, which ultimately may improve adherence to treatment and outcomes.

Comparing across trials, although atropine was prescribed daily in PEDIG 2002 and twice-weekly in Tejedor 2008, the magnitude of improvement in visual acuity in amblyopic eyes treated by atropine was comparable between these two trials. This was not unexpected. PEDIG 2004 demonstrated that weekend atropine provided a similar improvement in vision to daily atropine for participants aged between three and seven years with moderate amblyopia. Interestingly, the magnitude of improvement differed substantially in eyes treated by conventional occlusion. The inherent clinical heterogeneity between the two trials may explain some of these observed differences. First, the two trials used different patching protocols. PEDIG 2002 prescribed a minimum of six hours daily occlusion with 20% participants prescribed 12 hours over the initial six-month period. Excellent adherence as judged by PEDIG investigators was documented in 49% of cases. Tejedor 2008 used partial occlusion by positive defocusing of the sound eye. One of the main weaknesses of the latter study was adherence assessment, which was not easy to address for the partial occlusion because of difficulty in reporting frequency of peeking over glasses. It was therefore likely that the effects of partial occlusion were compromised by poor adherence. In addition, Tejedor 2008 lost 10% (7/70) of total participants. The analyses ignored issues arising from missing data. Moreover, these two trials included slightly different study populations. Children in Tejedor 2008 were one year older on average. Fifty-one per cent of children in Tejedor 2008 had strabismus as the cause of amblyopia, compared to 38% in PEDIG 2002. Baseline visual acuity in the amblyopic eye was 0.42 LogMAR in Tejedor 2008 and 0.51 LogMAR in PEDIG 2002. Older age at commencement of treatment, worse starting visual acuity, and strabismus as the cause of amblyopia have been related to poorer response to amblyopia treatment (Flynn 1998; Hiscox 1992; Newman 1996; Woodruff 1994). Consequently, these observed differences in the distribution of baseline characteristics may explain to some extent the heterogenous treatment effect observed in the conventional occlusion arm of the two trials.

Quality of the evidence

In addition to the small number of trials and different follow-up examination times, limitations to the evidence also stemmed from the clinical heterogeneity and the methodological quality of the included trials. Clinical heterogeneity was reflected in differences in the study populations, including the age of participants, baseline visual acuity, etiology of amblyopia, previous amblyopia treatment, and variations in the treatment regimens. Such clinical heterogeneity and methodological limitations made it problematic to combine the effect estimates from individual studies to estimate an overall effect in meta-analyses.

Potential biases in the review process

We worked with an Information Specialist to conduct a sensitive search of the literature. Two review authors independently completed all steps outlined in the Methods section of this review to reduce bias and errors.

Agreements and disagreements with other studies or reviews

We searched a database of systematic reviews in eyes and vision maintained by the Cochrane Eyes and Vision United States Satellite and identified no other reviews comparing patching to atropine penalization with which to compare our review findings. An overview of reviews (West 2016), which included the original version of this review, provided summary evidence for glasses, occlusion, and atropine penalization as the three treatment options for children with amblyopia; however, this overview provided no new information for our comparison of interest.

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AUTHORS' CONCLUSIONS

Implications for practice

This updated systematic review provides a summary of available evidence for doctors, patients, and other healthcare professionals about the effectiveness and safety of conventional occlusion versus atropine penalization for treating amblyopia. Current research suggests that atropine is probably as effective as conventional occlusion for the treatment of amblyopia.

- Atropine penalization provides similar improvement in visual acuity as conventional occlusion for moderate amblyopia in children.
- Atropine penalization may provide somewhat greater improvement in visual acuity compared to conventional occlusion for moderate amblyopia; however, this possibility should be interpreted with caution due to the small sample sizes and methodological limitations of the trials.
- There is no evidence of difference in ocular alignment and stereo acuity outcomes between atropine penalization and conventional occlusion.
- Adherence to treatment regimens was somewhat better among those participants prescribed atropine penalization compared to conventional occlusion.
- Atropine penalization had higher reported rates of adverse events, especially mild reduction of visual acuity in the sound eye that did not require treatment and increased light sensitivity (which was not reported for any participants receiving patching therapy).

Implications for research

The first published version of this systematic review (2009) identified key gaps in research, including the following.

- Long-term stability of treated amblyopia and the risk of recurrence of amblyopia.
- Comparison between different methods of occlusion to determine whether they are comparable, such as partial occlusion and total occlusion.
- Improved methods of documenting adherence to treatment, especially for those undergoing conventional occlusion.
- Further research into the effect of age, type of amblyopia, and density of amblyopia for both atropine and conventional occlusion.
- Cost-effectiveness analyses comparing atropine penalization and conventional occlusion, including parents' time, cost of patches/atropine, and time and cost associated with physician visits.

In this review update, long-term data regarding stability of treated amblyopia are now available and suggest no evidence of a difference between occlusion and atropine penalization by 10 or 15 years of age. All new studies in this update employed total occlusion regimens, and none employed partial occlusion regimens, thus we are unable to compare different occlusion methods. In this update, we did not find additional data beyond that from the original review on improved methods of documenting adherence; the effects of age, type of amblyopia, or density of amblyopia on atropine or occlusion; or cost-effectiveness. Dose monitor patches have been used for research but are not as yet clinically widely available at an affordable cost (Stewart 2017). We will continue to update this review as new evidence becomes available.

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REFERENCES

References to studies included in this review

Foley-Nolan 1997 *{published data only}*

Foley-Nolan A, McCann A, O'Keefe M. Atropine penalisation versus occlusion as the primary treatment for amblyopia. *British Journal of Ophthalmology* 1997;**81**(1):54-7.

Medghalchi 2011 *{published data only}*

Medghalchi A, Dalili S. A randomized trial of atropine versus patching for treatment of moderate amblyopia. *Iranian Red Crescent Medical Journal* 2011;**13**(8):7-9.

Menon 2008 *{published data only}*

Menon V, Shailesh G, Sharma P, Saxena R. Clinical trial of patching versus atropine penalization for the treatment of anisometropic amblyopia in older children. *Journal of AAPOS* 2008;**12**(5):493-7.

PEDIG 2002 *{published data only}*

Hertle RW, Scheiman MM, Beck RW, Chandler DL, Bacal DA, Birch E, et al. Stability of visual acuity improvement following discontinuation of amblyopia treatment in children aged 7 to 12 years. *Archives of Ophthalmology* 2007;**125**(5):655-9.

Holmes JM, Beck RW, Kraker RT, Astle WF, Birch EE, Cole SR, et al. Risk of amblyopia recurrence after cessation of treatment. *Journal of AAPOS* 2004;**8**(5):420-8.

Holmes JM, Beck RW, Kraker RT, Cole SR, Repka MX, Birch EE, et al. Impact of patching and atropine treatment on the child and family in the amblyopia treatment study. *Archives of Ophthalmology* 2003;**121**(11):1625-32.

Pediatric Eye Disease Investigator Group. A comparison of atropine and patching treatments for moderate amblyopia by patient age, cause of amblyopia, depth of amblyopia, and other factors. *Ophthalmology* 2003;**110**(8):1632-7.

Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Archives of Ophthalmology* 2002;**120**(3):268-78.

Pediatric Eye Disease Investigator Group. The clinical profile of moderate amblyopia in children younger than 7 years. *Archives of Ophthalmology* 2002;**120**(3):281-7.

Pediatric Eye Disease Investigator Group. The course of moderate amblyopia treated with atropine in children: experience of the amblyopia treatment study. *American Journal of Ophthalmology* 2003;**136**(4):630-9.

Pediatric Eye Disease Investigator Group. The course of moderate amblyopia treated with patching in children: experience of the amblyopia treatment study. *American Journal of Ophthalmology* 2003;**136**(4):620-9.

Repka MX, Holmes JM, Melia BM, Beck RW, Gearinger MD, Tamkins SM, et al. Pediatric Eye Disease Investigator Group. The effect of amblyopia therapy on ocular alignment. *Journal of AAPOS* 2005;**9**(6):542-5.

Repka MX, Kraker RT, Beck RW, Holmes JM, Cotter SA, Birch EE, et al. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs patching for treatment of moderate amblyopia: follow-up at age 10 years. *Archives of Ophthalmology* 2008;**126**(8):1039-44.

Repka MX, Kraker RT, Holmes JM, Summers AI, Barnhardt CN, Tien DR, et al. Pediatric Eye Disease Investigator Group. A randomized trial of atropine versus patching for treatment of moderate amblyopia: follow-up at 15 years of age. *Journal of AAPOS* 2014;**18**(4):e9.

Repka MX, Kraker RT, Holmes JM, Summers AI, Glaser SR, Barnhardt CN, et al. Pediatric Eye Disease Investigator Group. Atropine vs patching for treatment of moderate amblyopia follow-up at 15 years of age of a randomized clinical trial. *JAMA Ophthalmology* 2014;**132**(7):799-805.

Repka MX, Melia M, Eibschitz-Tsimhoni M, London R, Magoon E, Pediatric Eye Disease Investigator Group. The effect on refractive error of unilateral atropine as compared with patching for the treatment of amblyopia. *Journal of AAPOS* 2007;**11**(3):300-2.

Repka MX, Wallace DK, Beck RW, Kraker RT, Birch EE, Cotter SA, et al. Two-year follow-up of a 6-month randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Archives of Ophthalmology* 2005;**123**(2):149-57.

Simon JW. A randomized trial of atropine vs patching for treatment of moderate amblyopia follow-up at age 10 years. *Evidence-Based Ophthalmology* 2008;**10**(1):22.

PEDIG 2008 *{published data only}*

Felius J, Chandler DL, Holmes JM, Chu RH, Cole SR, Hill M, et al. Evaluating the burden of amblyopia treatment from the parent and child's perspective. *Journal of AAPOS* 2010;**14**(5):389-95.

O'Connor MD. Patching vs atropine to treat amblyopia in children aged 7 to 12 years. *Evidence-Based Ophthalmology* 2009;**10**(2):82-3.

Repka MX, Kraker RT, Beck RW, Birch E, Cotter SA, Holmes JM, et al. Pediatric Eye Disease Investigator Group. Treatment of severe amblyopia with atropine: results from two randomized clinical trials. *Journal of AAPOS - 35th Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus, San Francisco, CA United States* 2009;**13**(1):e9.

Repka MX, Kraker RT, Beck RW, Birch E, Cotter SA, Holmes JM, Pediatric Eye Disease Investigator Group. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *Journal of AAPOS* 2009;**13**(3):258-63.

Scheiman MM, Hertle RW, Kraker RT, Beck RW, Birch EE, Felius J, et al. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. *Archives of Ophthalmology* 2008;**126**(12):1634-42.

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Tejedor 2008 *{published and unpublished data}*

Tejedor J, Ogallar C. Comparative efficacy of penalization methods in moderate to mild amblyopia. *American Journal of Ophthalmology* 2008;**145**(3):562-9.

Yan 2008 *{published data only}*

Yan JJ, Peng HC, Wu CX, Liu ZY, Wang YF. A clinical trial of atropine penalization vs patching for treatment of monocular amblyopia. *International Journal of Ophthalmology* 2008;**8**(4):777-8.

References to studies excluded from this review

Chatzistefanou 2000 *{published data only}*

Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatric Drugs* 2000;**2**(2):91-100.

Cole 2001 *{published data only}*

Cole SR, Beck RW, Moke PS, Celano MP, Drews CD, Repka MX, et al. The Amblyopia Treatment Index. *Journal of AAPOS* 2001;**5**(4):250-4.

Huang 2009 *{published data only}*

Huang Y, Yang J, Zhang D, Shen P. Comparison between blinkers eyeshade occlusion and atropine therapy for the treatment of ametropic amblyopia. *International Journal of Ophthalmology* 2009;**9**(8):1615-7.

Liao 2009 *{published data only}*

Liao MY, Gao J, He Y. Effect of atropine combined with short-time occlusion for treating anisometropia amplyopia. *International Journal of Ophthalmology* 2009;**9**(7):1394-5.

PEDIG 2011 *{published data only}*

Wallace DK, Kraker RT, Beck RW, Cotter SA, Davis PL, Holmes JM, et al. Randomized trial to evaluate combined patching and atropine for residual amblyopia. *Archives of Ophthalmology* 2011;**129**(7):960-2.

Wallace DK, Kraker RT, Davis PL, Holmes JM, Repka MX, Suh DW. A randomized trial to evaluate combined patching and atropine for residual amblyopia. *Journal of AAPOS - 36th Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus Orlando, FL United States* 2009;**14**(1):e9.

PEDIG 2013 *{published data only}*

Wallace DK, Lazar EL, Repka MX, Holmes JM, Kraker RT, Hoover DL, et al. Augmenting atropine treatment for amblyopia in children 3 to < 8 years old (ATS16). *Journal of AAPOS* 2015;**19**(1):42-8.

Scheiman 2005 *{published data only}*

Scheiman MM, Hertle RW, Beck RW, Edwards AR, Birch E, Cotter SA, et al. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Archives of Ophthalmology* 2005;**123**(4):437-47.

Wu 2006 *{published data only}*

Wu C, Hunter DG. Amblyopia: diagnostic and therapeutic options. *American Journal of Ophthalmology* 2006;**141**(1):175-84.

Additional references

AAO 2012

American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus Panel. Preferred Practice Pattern® Guidelines. Amblyopia. San Francisco, CA: American Academy of Ophthalmology; 2012. www.aao.org/ppp.

Ansons 2001

Ansons A, Davis H. Diagnosis and Management of Ocular Motility Disorders. 3rd Edition. Oxford: Blackwell Science, 2001.

Antonio-Santos 2014

Antonio-Santos A, Vedula SS, Hatt SR, Powell C. Occlusion for stimulus deprivation amblyopia. *Cochrane Database of Systematic Reviews* 2014, Issue 2. [DOI: 10.1002/14651858.CD005136.pub2]

AOA 2004

Rouse MW, Cooper JS, Cotter SA, Press LJ, Tannen BM. Care of the patient with amblyopia: reference guide for clinicians. Revised October 1998, reviewed 2004. www.aoa.org/documents/CPG-4.pdf.

Attebo 1998

Attebo K, Mitchell P, Cumming R, Smith W, Jolly N, Sparkes R. Prevalence and causes of amblyopia in an adult population. *Ophthalmology* 1998;**105**(1):154-9.

Brown 2000

Brown SA, Weih LM, Fu CL, Dimitrov P, Taylor HR, McCarty CA. Prevalence of amblyopia and associated refractive errors in an adult population in Victoria, Australia. *Ophthalmic Epidemiology* 2000;**7**(4):249-58.

Ciuffreda 1991

Ciuffreda KJ, Levis DM, Selenow A. Amblyopia: Basic and Clinical Aspects. Boston: Butterworth-Heinemann, 1991.

Covidence 2019 [Computer program]

Veritas Health Innovation. Covidence systematic review software. Version available at: www.covidence.org. Melbourne, Australia: Veritas Health Innovation, 2019.

Deeks 2017

Deeks JJ, Higgins JP, Altman DG, editor(s) on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). The Cochrane Collaboration, 2017. Available from www.training.cochrane.org/handbook.

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Fells 1990

Fells P. Richardson Cross Lecture 1989 amblyopia — an historical perspective. *Eye* 1990;**4**(Pt 6):775-86.

Flom 1985

Flom MC, Bedell HE. Identifying amblyopia using associated conditions, acuity, and nonacuity features. *American Journal of Optometry and Physiological Optics* 1985;**62**(3):153-60.

Flynn 1998

Flynn JT, Schiffman J, Feuer W, Corona A. The therapy of amblyopia: an analysis of the results of amblyopia therapy utilizing the pooled data of published studies. *Transactions of American Ophthalmological Society* 1998;**96**:431-50.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;**94**(2):130-6.

Higgins 2017

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). The Cochrane Collaboration, 2017. Available from www.training.cochrane.org/handbook.

Hiscox 1992

Hiscox F, Strong N, Thompson JR, Minshull C, Woodruff G. Occlusion for amblyopia: a comprehensive survey of outcome. *Eye* 1992;**6**(3):300-4.

Jones 2003

Jones D, Westall C, Averbeck K, Abdolell M. Visual acuity assessment: a comparison of two tests for measuring children's vision. *Ophthalmic and Physiological Optics* 2003;**23**(6):541-6.

Kaye 2002

Kaye SB, Chen SI, Price G, Kaye LC, Noonan C, Tripathi A, et al. Combined optical and atropine penalization for the treatment of strabismic and anisometropic amblyopia. *Journal of AAPOS* 2002;**6**(5):289-93.

Levi 2006

Levi DM. Visual processing in amblyopia: human studies. *Strabismus* 2006;**14**(1):11-9.

Moseley 2002

Moseley MJ, Neufield M, McCarry B, Charnock A, McNamara R, Rice T, et al. Remediation of refractive amblyopia by optical correction alone. *Ophthalmic and Physiological Optics* 2002;**22**(4):296-9.

Newman 1996

Newman DK, Hitchcock A, McCarthy H, Keast-Butler J, Moore AT. Preschool vision screening: outcome of children referred to the hospital eye service. *British Journal of Ophthalmology* 1996;**80**(12):1077-82.

Newsham 2000

Newsham D. Parental non-concordance with occlusion therapy. *British Journal of Ophthalmology* 2000;**84**(9):957-62.

PEDIG 2004

Repka MX, Cotter SA, Beck RW, Kraker RT, Birch EE, Everett DF, et al. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. *Ophthalmology* 2004;**111**(11):2076-85.

PEDIG 2006

Wallace DK, Edwards AR, Cotter SA, Beck RW, Arnold RW, et al. Pediatric Eye Disease Investigator Group. A randomized trial to evaluate 2 hours of daily patching for strabismic and anisometropic amblyopia in children. *Ophthalmology* 2006;**113**(6):904-12.

PEDSG 2008

Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of amblyopia and strabismus in African and Hispanic children ages 6 to 72 months: The Multi-ethnic Pediatric Eye Disease Study. *Ophthalmology* 2008;**115**(7):1229-36.

PEDSG 2013

Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of amblyopia or strabismus in Asian and non-Hispanic white preschool children: Multi-ethnic Pediatric Eye Disease Study. *Ophthalmology* 2013;**120**(10):2117-24.

Rahi 2002

Rahi J, Logan S, Timms C, Russell-Eggitt I, Taylor D. Risks, causes and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population based study. *Lancet* 2002;**360**(9333):597-602.

Repka 1993

Repka MX, Ray JM. The efficacy of optical and pharmacological penalization. *Ophthalmology* 1993;**100**(5):769-75.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

Simons 1996

Simons K. Preschool vision screening: rationale, methodology and outcome. *Survey of Ophthalmology* 1996;**41**(1):3-30.

Simons 1997

Simons K, Stein L, Sener EC, Vitale S, Guyton DL. Full-time atropine, intermittent atropine, and optical penalization and binocular outcome in treatment of strabismic amblyopia. *Ophthalmology* 1997;**104**(12):2145-55.

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Simons 1999

Simons K, Preslan M. Natural history of amblyopia owing to lack of compliance. *British Journal of Ophthalmology* 1999;**83**(5):582-7.

Simons 2005

Simons K. Amblyopia characterization, treatment, and prophylaxis. *Survey of Ophthalmology* 2005;**50**(2):123-66.

Stewart 2017

Stewart CE, Mosely MJ, Georgiou P, Fielder AR. Occlusion dose monitoring in amblyopia therapy: status, insights, and future directions. *Journal of AAPOS* 2017;**21**(5):402-6.

Swann 1974

Swann AP, Hunter CD. A survey of amblyopia treated by atropine occlusion. *British Orthoptic Journal* 1974;**31**:65-9.

Taylor 2012

Taylor K, Powell C, Hatt SR, Stewart C. Interventions for unilateral and bilateral refractive amblyopia. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD005137.pub3]

Taylor 2014

Taylor K, Elliott S. Interventions for strabismic amblyopia. *Cochrane Database of Systematic Reviews* 2014, Issue 7. [DOI: 10.1002/14651858.CD006461.pub3]

Tommila 1981

Tommila V, Tarkkannen A. Incidence of loss of vision in the healthy eye in amblyopia. *British Journal of Ophthalmology* 1981;**65**(8):575-7.

West 2016

West S, Williams C. Amblyopia in children (aged 7 years or less). *BMJ Clinical Evidence* 2016;**01**:0709.

Williams 2002

Williams C, Northstone K, Harrad RA, Sparrow JM, Harvey I, ALSPAC Study Team. Amblyopia treatment outcomes after screening before or at age 3 years: follow up from randomised trial. *BMJ* 2002;**324**(7353):1549.

Woodruff 1994

Woodruff F, Hiscox F, Thompson JR, Smith LK. Factors affecting the outcome of children treated for amblyopia. *Eye* 1994;**8**(Pt 6):627-31.

References to other published versions of this review

Li 2009

Li T, Shotton K. Conventional occlusion versus pharmacologic penalization for amblyopia. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD006460.pub2]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Foley-Nolan 1997

Methods	Study design: CCT
	Number randomized: 36 (18 in the occlusion group; 18 in the atropine penalization group)
	Unit of randomization: 1 eye per participant was randomized.
	Number analyzed: 36
	Number of centers: 1
	Date of first enrollment: January 1994
	Length of follow-up: planned: unclear; actual: unclear
	Sample size estimation: not reported
Participants	Country: Ireland
	Age: mean 5.5 years (range 2.5 to 9 years)
	Sex: not reported
	Key inclusion criteria: any type or level of amblyopia; no previous treatment for amblyopia
	Key exclusion criteria: none reported
	Frequency of strabismus as the cause of amblyopia: 92% (including participants affected by combined-mechanism amblyopia)

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Foley-Nolan 1997 *(Continued)*

	Baseline visual acuity in the amblyopic eye: 0.92 LogMAR in atropine penalization group; 1 LogMAR in occlusion group Comparability of baseline characteristics: comparable
Interventions	Intervention regimen #1: occlusive patch placed over sound eye. Regimen of occlusion varies by age and level of amblyopia. Full-time occlusion was instigated for 1 week per year of life. Once vision improved to 6/9 or better, occlusion was reduced to half day. Participants monitored weekly per year of life. Treatment was concluded when a visual acuity of 6/6 was achieved, or when visual acuity remained static over 3 successive assessments. Intervention regimen #2: atropine drops 1% instilled daily (every morning) into sound eye. Follow-up visits approximately once a month. Treatment was concluded when a visual acuity of 6/6 was achieved, or when visual acuity remained static over 3 successive assessments.
Outcomes	Visual acuity assessed using the Snellen chart, Kay's Pictures, or Sheridan-Gardiner test types, depending on the age and comprehension of the participant. Refractive error examined by cycloplegic retinoscopy 35 minutes after instillation of 1% cyclopentolate.
Notes	Funding sources: none declared Statistical analyses: inappropriate (no between-group comparison was made) Subgroup analyses: none reported Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"All new patients due to commence treatment for amblyopia were allocated either to treatment with atropine penalization, or to occlusion therapy. This was achieved on a strict alternate patient basis."
Allocation concealment (selection bias)	High risk	"Appointments were organized by an independent observer (clinic sister) in order to prevent any possibility of bias being introduced."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The visual acuity assessors were masked to patient treatment."
Incomplete outcome data (attrition bias) Primary outcome: visual acuity	Low risk	No lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess
Other bias	High risk	Sample size was very small to detect any meaningful difference. Inappropriate statistical analyses

Medghalchi 2011

Methods	Study design: CCT

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Medghalchi 2011 *(Continued)*

	Number randomized: unclear (only reported number of participants with 2 years follow-up) Unit of randomization: 1 eye per participant was randomized. Number analyzed: 120 (60 in the occlusion group; 60 in the atropine penalization group) Number of centers: 1 Date of first enrollment: January 2004 Length of follow-up: planned: 2 years; actual: 2 years Sample size estimation: not reported
Participants	Country: Iran Age: mean: not reported; range: 4 to 10 years Sex: 55% male; 45% female Key inclusion criteria: 4 to 10 years; visual acuity of amblyopic eye between 20/40 and 20/100; intereye visual acuity difference of ≥ 3 LogMAR lines; intereye refractive error difference ≥ 1 D for hyperopia and 1.5 D for astigmatism; wearing of optical correction for at least 4 weeks; at least 2 years follow-up Key exclusion criteria: none reported Frequency of strabismus as the cause of amblyopia: not reported Baseline visual acuity in the amblyopic eye: 0.45 in occlusion group, 0.45 in atropine penalization group Comparability of baseline characteristics: comparable
Interventions	Intervention regimen #1: patching therapy. Dose varied depending on difference in vision: in participants with 2 lines acuity difference between eyes, 2 hours patch therapy was performed; in those with 3 or more lines difference, 3 hours patch therapy was started. Frequency of follow-up, treatment duration, or alterations to treatment not reported. Intervention regimen #2: atropine penalization. 0.5% atropine twice a week. During improvement of the VA, the penalization dose decreased to 1 drop weekly. Frequency of follow-up, treatment duration, or alterations to treatment not reported.
Outcomes	Primary outcome: improvement in visual acuity of the amblyopic eye at 2 years, defined as 2 or more lines improvement or visual acuity of 20/25 or better, measured by Snellen or LogMAR Outcomes reported: stereo acuity
Notes	Funding sources: none declared Statistical analyses: appropriate Subgroup analyses: none reported Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Randomization was done on the patients records, the even number assigned to 3 hours patch therapy and odd numbers for those undergone penalization with 0.5% atropine twice a week."

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Medghalchi 2011 *(Continued)*

Allocation concealment (selection bias)	High risk	Allocation was not concealed as it was determined by the patients' record numbers.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No masking was done.
Incomplete outcome data (attrition bias) Primary outcome: visual acuity	Unclear risk	Only participants with 2 years follow-up were included in the report and analyses. The number of participants assessed and enrolled in the study was not reported. It is unclear whether any participants had less that 2 years follow-up and were excluded
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess
Other bias	Low risk	No other sources of bias identified

Menon 2008

Methods	Study design: RCT Number randomized: 63 (32 in the occlusion group; 31 in the atropine penalization group) Unit of randomization: 1 eye per participant was randomized. Number analyzed: 57 (29 in the occlusion group; 28 in the atropine penalization group). 6 participants (3 in each group) were excluded from analyses because of incomplete follow-up after their second visit. Number of centers: 1 Date of first enrollment: not reported Length of follow-up: planned: unclear; actual: 6 months Sample size estimation: the investigator did not perform sample size calculations in advance of the study. The authors stated that "...as we were aware in advance that we would be recruiting as many patients as possible over a period of three years in a single centre." The power of the study for the final visual acuity was found to be 6% at the end of the trial.
Participants	Country: India Age (mean ± SD): 13.53 ± 4.01 in the occlusion group; 13.75 ± 3.66 in the atropine penalization group; (range 8 to 20 years) Sex: not reported Key inclusion criteria: anisometropic hypermetropia of more than 1 D; intereye visual acuity difference of ≥ 3 LogMAR lines; visual acuity in sound eye of > 6/9; visual acuity of amblyopic eye between 6/12 and 6/60 Key exclusion criteria: myopia; more than 2 months of amblyopia therapy in the past 2 years; and a known skin reaction to patches or allergy to atropine Frequency of strabismus as the cause of amblyopia: 0% Baseline visual acuity in the amblyopic eye: 0.221 modified LogMAR in occlusion group, 0.228 modified LogMAR in atropine penalization group

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Menon 2008 *(Continued)*

	Comparability of baseline characteristics: refractive error was statistically significantly worse in the patching group (P = 0.027)
Interventions	Intervention regimen #1: "Full-time patching of the sound eye using Micropore tape (3M, St.Paul, MN) attached to a piece of opaque oval paper". Patching was alternated between the sound eye and amblyopic eye with 6:1 ratio (i.e. patching of the sound eye for 6 days followed by patching of the amblyopic eye for 1 day). If allergy to Micropore developed, it was replaced with Doyne's occluder or Opticlude (Nexcare, 3M). Intervention regimen #2: 1 drop per day of atropine sulphate 1% in the sound eye. Punctal occlusion used to prevent systemic absorption and excess atropine wiped away to prevent allergic reaction. If allergy to atropine developed, it was replaced with homatropine 2%. Daily use continued until visual acuity reached the desired level (not specified), or if there was no improvement in visual acuity for 3 months, at which point a minimum twice-weekly regimen was adopted.
Outcomes	Primary outcome: visual acuity in the amblyopic eye after 6 months of treatment, measured by Snellen chart at 6 meters test distance. The ETDRS chart also was used to record visual acuity in LogMAR at 4 meters test distance. Outcomes reported: near vision, measured with point system (printer's type) and converted to decimal notation; contrast sensitivity, measured with Pelli-Robson chart at 1 meter test distance; stereo acuity, measured with TNO; compliance, measured by parent and patient interview; and harms
Notes	Funding sources: not reported Statistical analyses: P values rather than effect estimates and confidence intervals were reported. Subgroup analyses: performed by baseline visual acuity in amblyopic eye (6/60 to 6/24 vs 6/18 to 6/24) Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were divided into 2 main treatment groups: a patching group (P), which received full-time conventional patching, and an atropine group (A), which received penalization with atropine. Stratified randomization was used to place patients in these 2 groups, which were further divided into 2 subgroups, depending on the visual acuity of patients at presentation"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking not reported
Incomplete outcome data (attrition bias) Primary outcome: visual acuity	High risk	6 participants, 3 from each group, were excluded due to incomplete follow-up after the second visit. They were considered treatment failures and not included for analysis. Long distance and travel time were the reasons for lack of follow-up.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess
Other bias	High risk	Funding source not reported; patching group had higher refractive error at baseline

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PEDIG 2002

Methods	Study design: RCT Number randomized: 419 (215 in the occlusion group; 204 in the atropine penalization group). Based on a postrandomization review, 10 patients (3 in the occlusion and 7 in the atropine group) did not fully meet the eligibility criteria. Unit of randomization: 1 eye per participant was randomized. Number analyzed: 419 Number of centers: 47 (number of patients enrolled per site ranged from 1 to 35, median = 5 patients) Date of first enrollment: April 1999 Length of follow-up: planned: 2 years; actual: 2 years Sample size estimation: the sample size was based on whether the visual improvement at 6 months with atropine was equivalent to that with patching (equivalent level of the 95% CI for the difference in mean visual acuity between groups was set to be 0.1 LogMAR unit; power = 80% and α = 0.05 for assessments of the treatment group differences in each of 3 subgroups based on cause of amblyopia). With the sample size estimated n = 400, the power for the primary overall analysis was 99%.
Participants	Country: United States Age (mean ± SD): 5.3 ± 1.1 years Sex: 47% were girls Key inclusion criteria: age < 7; able to measure visual acuity using the Amblyopia Treatment Study Visual Acuity testing protocol; visual acuity in the amblyopic eye ≤ 20/40 and ≥ 20/100; visual acuity in the sound eye ≥ 20/40; intereye acuity difference ≥ 3 LogMAR lines; no more than 2 months of amblyopia therapy in the past 2 years; refractive error corrected for at least 4 weeks; amblyopia associated with strabismus, refractive error/anisometropia, or both Key exclusion criteria: presence of an ocular cause for reduced visual acuity; prior intraocular surgery; myopia (spherical equivalence of −0.50 D or more) in either eye; Down syndrome; known skin reaction to patch or bandage adhesive, or allergy to atropine or other cycloplegics Frequency of strabismus as the cause of amblyopia: 38% Baseline visual acuity in the amblyopic eye: 0.53 LogMAR in atropine penalization group, 0.52 LogMAR in occlusion group Comparability of baseline characteristics: comparable
Interventions	Intervention regimen #1: conventional occlusion prescribed for minimum of 6 hours daily and maximum all waking hours. This continued for full 6 months unless occlusion amblyopia developed. When criteria for successful result was met, occlusion was then reduced but needed to be minimum of 7 hours per week. Where there was visual acuity difference of 1 line (i.e., when equal visual acuity was achieved) occlusion was stopped. If criteria for successful treatment were not met by the 16-week visit, and patching time had been less than 12 hours per day, patching time was increased to 12 or more hours per day for 2 months prior to the 6-month outcome examination. Adhesive skin patches provided by the study (Coverlet Eye Occlusors; Beiersdorf-Jobst Inc, Rutherford College, NC) were used unless there was skin allergy or irritation non-responsive to both local treatment with a skin emollient and a change in the brand of patch, in which case a spectacle occluder could be prescribed. Intervention regimen #2: 1 drop per day of atropine sulphate 1%. Daily use continued until successful visual acuity outcomes achieved. Atropine could then be reduced to twice weekly or discontinued. For participants with hyperopia in the sound eye, if the amblyopic eye was not successfully treated by the

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PEDIG 2002 *(Continued)*

	16-week visit, the spectacle lens was reduced to plano for 2 months prior to the 6-month outcome examination. If allergy development, treatment was changed to 5% homatropine.
Outcomes	Primary outcome: amblyopic eye visual acuity score in LogMAR units measured using Amblyopia Treatment Study visual acuity testing protocol at 6 months Secondary outcomes: 1. Treatment success defined as a 6-month visual acuity of 20/30 or better and/or improved from baseline by 3 or more lines (a participant was classified as a treatment failure if the success criteria were not met or if the non-assigned treatment was received for at least 1 week). 2. Amblyopic eye visual acuity score in LogMAR units at 2 years 3. Visual acuity in the sound eye at 2 years 4. Ocular alignment at 2 years 5. Stereo acuity at 2 years
Notes	Funding sources: National Eye Institute, National Institutes of Health, Bethesda, MD, USA. Companies provided materials at a discount for the study: Precision Vision (near acuity test), Stereo Optical Co Inc (stereo acuity tests), Beiersdorf-Jobst Inc (Coverlet Eye Occlusors), and Bausch and Lomb Pharmaceuticals Inc (atropine). Statistical analyses: appropriate Subgroup analyses: reported Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was accomplished on the study's web site using a permuted-blocks design of varying block sizes with a separate sequence of computer-generated random numbers for each investigator."
Allocation concealment (selection bias)	Low risk	"Randomization was accomplished on the study's web site," which is 1 form of central allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"At the 6-month outcome examination, visual acuity testing of the amblyopic eye was conducted by a tester masked to the patient's treatment group. To conceal the treatment group assignment, a patch was placed over the sound eye by site staff prior to the examination to avoid unmasking either from a dilated pupil due to atropine or from skin changes due to patching." "At the 2-year examination, a tester masked to the patient's treatment group conducted visual acuity testing." The vision tester was masked to treatment group for 97% of these examinations at 6 months, and 92% at 24 months.
Incomplete outcome data (attrition bias) Primary outcome: visual acuity	Low risk	At 6 months: Patching group: 7 dropped out in total (4 lost to follow-up, 3 were withdrawn at the request of the parent); 208/215 = 97% completed. Atropine group: 10 dropped out in total (6 lost to follow-up, 4 were withdrawn at the request of the parent); 194/204 = 95% completed. "All analyses followed the intention-to-treat principle." "Patients were included in the primary analysis if they had a visual acuity measurement in the amblyopic eye within the time window of the 6-month visit or, in the absence of such a visit, if they had a visual acuity measurement that was no more than 1 month before or 3 months after this window. Two additional analyses were conducted on the 6-month amblyopic eye LogMAR acuity scores: one analysis included only patients who had an examination with-

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PEDIG 2002 *(Continued)*

		in the 6-month window, and the other analysis included all patients using the method of last observation carried forward to impute for missing data (for patients missing the outcome examination, the visual acuity recorded at the last follow-up examination was used; for patients with no follow-up, the baseline acuity was used). Results of these 2 analyses were similar to the primary analysis (data not shown)."
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias found.
Other bias	Low risk	No other sources of bias identified.

PEDIG 2008

Methods	Study design: RCT Number randomized: 193 (98 in the occlusion group; 95 in the atropine penalization group) Unit of randomization: 1 eye per participant was randomized. Number analyzed: 180 (91 in the occlusion group; 89 in the atropine penalization group) at 5 weeks and 172 (84 in the occlusion group; 88 in the atropine penalization group) at 17 weeks Number of centers: 39 Date of first enrollment: 1 August 2005 Length of follow-up: planned: 17 weeks; actual: 17 weeks Sample size estimation: the trial was designed to evaluate whether patching and atropine are equivalent treatments for amblyopia in children aged 7 to 12 years. A sample size of 180 participants had 90% power and a type I error rate of 5% for an equivalence limit of 5 letters (1 line) based on the following assumptions: SD of 17-week visual acuity scores of 10 letters, correlation between outcome and baseline visual acuity scores of 0.30, and 10% unavailable for follow-up.
Participants	Country: United States Age (mean ± SD): 8.9 ± 1.5 in the occlusion group; 9.1 ± 1.6 in the atropine penalization group (range 7 to 12 years) Sex: 52.8% (102/193) female Key inclusion criteria: age 7 to 13 years; visual acuity in the amblyopic eye between 48 and 71 letters (20/40 to 20/100); visual acuity in the sound eye of 79 letters of better (≥ 20/25); an intereye visual acuity difference of 15 letters or more (≥ 3 lines); presence of or history of an amblyogenic factor meeting study-specified criteria for strabismus and/or anisometropia; and the wearing of optimal spectacle correction for a minimum of 16 weeks or until stability of visual acuity was documented Key exclusion criteria: myopia greater than a spherical equivalent of −0.25 D in either eye, treatment for amblyopia (other than spectacle correction) within the 6 months before enrollment, and Down syndrome Frequency of strabismus as the cause of amblyopia: 31.6% (61/193) Baseline visual acuity in the amblyopic eye: 62.4 ± 5.7 letters in occlusion group, 61.7 ± 6.6 letters in atropine penalization group Comparability of baseline characteristics: comparable
Interventions	Intervention regimen #1: occlusion with adhesive skin patches provided by Coverlet was initially prescribed for 2 hours of patching per day plus near visual tasks to be done while wearing the patch for

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PEDIG 2008 *(Continued)*

	at least 1 hour per day. If allergy or skin reaction to patch developed, local treatment with emollient, change of brand of patch, or spectacle occluder was used. At the 5-week visit, if the amblyopic eye acuity had not improved at least 5 letters from baseline, patching was increased to 4 hours per day. Treatment was continued or reduced to 1 hour per day if visual acuity reached 79 letters by week 5. Intervention regimen #2: 1 drop of atropine sulphate 1% placed in the sound eye on Saturday and Sunday of each week plus near visual tasks to be done at least 1 hour per day. If allergy to atropine developed, it was replaced by homatropine 5%. Sunglasses and brimmed hats were to be worn in sunlight. If reading glasses were prescribed, near activities were done without the use of reading glasses for at least an hour a day. If the amblyopic eye acuity had not improved at least 5 letters from baseline to the 5-week visit, atropine was increased to 1 drop in the sound eye daily. Treatment was not discontinued unless allergy developed.
Outcomes	Primary outcome: visual acuity measured using E-ETDRS testing procedure at 17-week visit Secondary outcomes: 1. Proportion of participants with 17-week visual acuity in the amblyopic eye of 20/25 of better 2. Proportion of participants with 17-week visual acuity in the amblyopic eye improved 15 or more letters from baseline 3. Stereo acuity at 17 weeks 4. Amblyopia Treatment Index
Notes	Funding sources: Grant EY011751, National Eye Institute, National Institutes of Health, Bethesda, MD, USA Statistical analyses: appropriate Subgroup analyses: none reported Registration: NCT00315328

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a permuted blocks design stratified by site and visual acuity in the amblyopic eye, data entered on the PEDIG Web site were used to randomly assign each participant to 1 of 2 treatment groups: atropine (1% each weekend day in the sound eye) or patching of the sound eye 2 hours per day."
Allocation concealment (selection bias)	Low risk	"Using a permuted blocks design stratified by site and visual acuity in the amblyopic eye, data entered on the PEDIG Web site were used to randomly assign each participant to 1 of 2 treatment groups: atropine (1% each weekend day in the sound eye) or patching of the sound eye 2 hours per day."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"At the 17-week visit, the examiner was masked to treatment group, and the sound eye was patched for patients in both groups before the examiner saw the patient."
Incomplete outcome data (attrition bias) Primary outcome: visual acuity	Low risk	At 17 weeks, 14/98 (14.3%) participants in the patching group and 7/95 (7.4%) in the atropine group were not included in the analysis. The study investigators reported that alternate analyses using the last-observation-carried-forward method to impute missing data showed similar results to the available-case data analyses.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the study protocol were reported.

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PEDIG 2008 *(Continued)*

Other bias	Unclear risk	Data were collected at different times (17 weeks vs 19 weeks) for the sound eye depending on treatment group.

Tejedor 2008

Methods	Study design: RCT Number randomized: 70 (35 in the optical penalization group; 35 in the atropine penalization group) Unit of randomization: 1 eye per participant was randomized. Number analyzed: 63 Number of centers: 1 Date of first enrollment: January 2004 Length of follow-up: planned: 6 months; actual: 6 months Sample size estimation: the sample size was based on 0.1 LogMAR units difference between the 2 groups in change in visual acuity of the amblyopic eye, an SD of 0.15, and a type I error of 5%. With the sample size estimated at 70, the power for the primary overall analysis was 98%.
Participants	Country: Spain Age (mean ± SD): 5.8 ± 2.12 years in the atropine group; 6.25 ± 2.11 years in the optical penalization group Sex: not reported Key inclusion criteria: anisometropia or strabismic amblyopia; 2 to 10 years of age; interocular difference in visual acuity was at least 2 LogMAR lines (0.2 LogMAR units); visual acuity in the amblyopic eye was at least 0.5 LogMAR Key exclusion criteria: children who have been previously treated for amblyopia; organic ocular disease; preceding ocular surgery or botulinum treatment; mixed amblyopia Frequency of strabismus as the cause of amblyopia: 51% Baseline visual acuity in the amblyopic eye: 0.41 LogMAR in atropine group; 0.44 LogMAR in optical penalization group Comparability of baseline characteristics: comparable
Interventions	Intervention regimen #1: optical penalization was achieved by positive defocus of the sound eye (over-plus glass). Sphere was added until vision in the sound eye was blurred to the same level as that of the amblyopic eye. Minimal amount of sphere needed was prescribed. Optical penalization was readjusted if necessary at every follow-up visit. Defocus was discontinued when visual acuity remained equal in the amblyopic and sound eye for 2 consecutive visits. Intervention regimen #2: 1% atropine drops (Colircusi Atropina 1%; AlconCusi, Barcelona, Spain) twice weekly when interocular acuity difference was present, and once weekly for maintenance therapy (equal visual acuity in both eyes) until the next follow-up visit. Atropine was withdrawn when visual acuity remained equal in the amblyopic and sound eye on 2 consecutive follow-up visits. Atropine was discontinued when allergy or intolerance occurred or when reverse amblyopia was suspected.
Outcomes	Primary outcome: change in visual acuity of the amblyopic eye at 6 months of treatment measured using the LogMAR Crowded Glasgow acuity cards

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Tejedor 2008 *(Continued)*

	Secondary outcomes: sensory status determined by stereo acuity measurement using the Titmus fly test and Randot preschool or Randot circles stereo acuity test
Notes	Funding sources: Fundación De Investigación Biomédica, Hospital Ramón Y Cajal, Madrid, Spain Statistical analyses: appropriate Subgroup analyses: based on types of amblyopia Registration: ISRCTN89210627

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomized to atropine or optical defocus, after stratification into two groups according to cause of amblyopia using a computer-generated sequence of random numbers, by the steering committee."
Allocation concealment (selection bias)	Low risk	"In this study a central office steering committee handled the randomization process so that investigators who determined eligibility and enrolled individuals were unaware of the assignment order." (Information source: personal contact with the lead investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Observers who measured visual acuity were masked to the treatment group. The reported success of blinding in 90.6% (29/32) of the optical and 87% (27/31) of the pharmacologic penalization groups."
Incomplete outcome data (attrition bias) Primary outcome: visual acuity	High risk	3 lost to follow-up in penalization group; 2 discontinued treatment in the atropine group because of intolerance, 1 was withdrawn, and 1 lost follow-up. These 7 participants were excluded from the analyses.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess
Other bias	Unclear risk	Unclear

Yan 2008

Methods	Study design: RCT Number randomized: 276 (135 in the occlusion group; 141 in the atropine penalization group) Unit of randomization: 1 eye per participant was randomized. Number analyzed: 276 Number of centers: 1 Date of first enrollment: February 2002 Length of follow-up: planned: unclear; actual: unclear Sample size estimation: not reported
Participants	Country: China Age: mean: 9.2 years; range: 7 to 14 years

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Yan 2008 *(Continued)*

	Sex: 53.3% (147/193) female Key inclusion criteria: monocular amblyopia; 7 to 14 years of age Key exclusion criteria: non-horizontal strabismus Frequency of strabismus as the cause of amblyopia: not reported Baseline visual acuity in the amblyopic eye: not reported Comparability of baseline characteristics: comparable
Interventions	Intervention regimen #1: occlusive patch placed for 6 hours per day. Treatment was concluded when a visual acuity of 0.9 LogMAR was achieved, or when visual acuity remained static for 3 months. Intervention regimen #2: 1% atropine eye ointment applied to the sound eye once every night. For refractive errors, full correction lenses were used for the sound eye and overcorrection lenses of +2.00 D were used for the amblyopic eye. Treatment was concluded when a visual acuity of 0.9 LogMAR was achieved, or when visual acuity remained static for 3 months.
Outcomes	Primary outcome: total effective rate, defined as LogMAR visual acuity of 0.9 or better, or an improvement of 2 or more lines of visual acuity Secondary outcomes: changes in ocular position, defined as 1) increase of strabismus degree of 8 or more, 2) decrease of strabismus degree of 8 or more, and 3) less than 8 change in strabismus degree, measured by synoptophore and triangular prism; participants' adherence to treatment, measured by daily evaluation forms completed by participants and parents of participants
Notes	Funding sources: not reported Statistical analyses: appropriate Subgroup analyses: none reported Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking not reported
Incomplete outcome data (attrition bias) Primary outcome: visual acuity	Low risk	All participants completed the study and there were no losses to follow-up, no treatment withdrawals, no trial group changes, and no major adverse events.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess
Other bias	Low risk	No other sources of bias identified.

CCT: controlled clinical trial

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CI: confidence interval
D: diopter
PEDIG: Pediatric Eye Disease Investigator Group
RCT: randomized controlled trial
SD: standard deviation
VA: visual acuity

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chatzistefanou 2000	Not a randomized controlled trial: narrative review article
Cole 2001	Not a randomized controlled trial: development of a questionnaire
Huang 2009	Not the comparison of interest: participants received atropine combined with patching in both study arms; intensity of treatment compared
Liao 2009	Not the comparison of interest: participants received atropine combined with patching in both study arms; intensity of patching compared
PEDIG 2011	Not the comparison of interest: participants received combined atropine and patching in same arm
PEDIG 2013	Not the comparison of interest: participants received atropine plus plano lens versus atropine alone; no patching arm
Scheiman 2005	Not the comparison of interest: participants received optical correction combined with atropine or optical correction alone
Wu 2006	Not a randomized controlled trial: narrative review article

DATA AND ANALYSES

Comparison 1. Conventional occlusion versus atropine penalization

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean difference in visual acuity at a follow-up time point	4		Mean Difference (Random, 95% CI)	Totals not selected
1.1 5-week follow-up	1		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
1.2 17-week follow-up	1		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
1.3 6-month follow-up	3		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
1.4 24-month follow-up	1		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
1.5 10 years of age	1		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
1.6 15 years of age	1		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 0.2 LogMAR (6/9 or 20/30 Snellen equivalent) or better visual acuity	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 At 5 weeks after initiation of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 At 17 weeks after initiation of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 At 6 months after initiation of therapy	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 At 24 months after initiation of therapy	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 2 or more lines improvement in visual acuity from baseline	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 At 5 weeks after initiation of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 At 17 weeks after initiation of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 At 6 months after initiation of therapy	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 At 24 months after initiation of therapy	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Within 2 lines of baseline visual acuity	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 At 5 weeks after initiation of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 At 17 weeks after initiation of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 At 6 months after initiation of therapy	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 At 24 months after initiation of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Adherence to treatment	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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Analysis 1.1. Comparison 1 Conventional occlusion versus atropine penalization, Outcome 1 Mean difference in visual acuity at a follow-up time point.

Study or subgroup	Conventional occlusion N	Atropine penalization N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.1.1 5-week follow-up					
PEDIG 2008	91	89	0 (0.016)		0.01[-0.02,0.05]
1.1.2 17-week follow-up					
PEDIG 2008	84	88	0 (0.019)		0.02[-0.01,0.06]
1.1.3 6-month follow-up					
Menon 2008	29	28	-0 (0.046)		-0.02[-0.11,0.07]
PEDIG 2002	208	194	0 (0.015)		0.03[0,0.06]
Tejedor 2008	32	31	-0.1 (0.046)		-0.14[-0.23,-0.05]
1.1.4 24-month follow-up					
PEDIG 2002	188	175	0 (0.015)		0.01[-0.02,0.04]
1.1.5 10 years of age					
PEDIG 2002	85	84	0 (0.026)		0.03[-0.02,0.08]
1.1.6 15 years of age					
PEDIG 2002	75	72	0 (0.026)		0.01[-0.04,0.06]
			Favors atropine	-0.2 -0.1 0 0.1 0.2	Favors occlusion

Analysis 1.2. Comparison 1 Conventional occlusion versus atropine penalization, Outcome 2 0.2 LogMAR (6/9 or 20/30 Snellen equivalent) or better visual acuity.

Study or subgroup	Conventional occlusion n/N	Atropine penalization n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.2.1 At 5 weeks after initiation of therapy				
PEDIG 2008	39/91	26/89		1.47[0.98,2.19]
1.2.2 At 17 weeks after initiation of therapy				
PEDIG 2008	39/84	36/88		1.13[0.81,1.6]
1.2.3 At 6 months after initiation of therapy				
PEDIG 2002	132/208	103/194		1.2[1.01,1.41]
Tejedor 2008	18/32	23/31		0.76[0.52,1.1]
1.2.4 At 24 months after initiation of therapy				
Medghalchi 2011	44/60	46/60		0.96[0.78,1.18]
PEDIG 2002	141/188	124/175		1.06[0.93,1.2]
		Favors atropine	0.5 0.7 1 1.5 2	Favors occlusion

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Analysis 1.3. Comparison 1 Conventional occlusion versus atropine penalization, Outcome 3 2 or more lines improvement in visual acuity from baseline.

Study or subgroup	Conventional occlusion n/N	Atropine penalization n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.3.1 At 5 weeks after initiation of therapy				
PEDIG 2008	30/91	25/89		1.17[0.75,1.83]
1.3.2 At 17 weeks after initiation of therapy				
PEDIG 2008	38/84	35/88		1.14[0.8,1.61]
1.3.3 At 6 months after initiation of therapy				
PEDIG 2002	181/208	160/194		1.06[0.97,1.15]
Tejedor 2008	18/32	27/31		0.65[0.46,0.9]
1.3.4 At 24 months after initiation of therapy				
Medghalchi 2011	44/60	46/60		0.96[0.78,1.18]
PEDIG 2002	170/188	152/175		1.04[0.97,1.12]
		Favours atropine	0.5 0.7 1 1.5 2	Favours occlusion

Analysis 1.4. Comparison 1 Conventional occlusion versus atropine penalization, Outcome 4 Within 2 lines of baseline visual acuity.

Study or subgroup	Conventional occlusion n/N	Atropine penalization n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.4.1 At 5 weeks after initiation of therapy				
PEDIG 2008	61/91	64/89		0.93[0.77,1.13]
1.4.2 At 17 weeks after initiation of therapy				
PEDIG 2008	45/84	51/88		0.92[0.71,1.21]
1.4.3 At 6 months after initiation of therapy				
PEDIG 2002	27/208	34/194		0.74[0.46,1.18]
Tejedor 2008	14/32	4/31		3.39[1.25,9.17]
1.4.4 At 24 months after initiation of therapy				
PEDIG 2002	18/188	22/175		0.76[0.42,1.37]
		Favors atropine	0.1 0.2 0.5 1 2 5 10	Favors occlusion

Analysis 1.5. Comparison 1 Conventional occlusion versus atropine penalization, Outcome 5 Adherence to treatment.

Study or subgroup	Conventional occlusion n/N	Atropine penalization n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Foley-Nolan 1997	10/18	17/18		0.59[0.38,0.9]
Menon 2008	18/29	16/28		1.09[0.71,1.67]
PEDIG 2002	102/208	151/194		0.63[0.54,0.74]
Tejedor 2008	27/32	27/31		0.97[0.79,1.18]
		Favours atropine	0.5 0.7 1 1.5 2	Favours occlusion

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ADDITIONAL TABLES

Table 1. Outcomes reported by study

Study	Mean VA	Categorical VA	Stero acuity	Ocular alignment	Adherence, QoL, or economic outcomes	Harms
Foley-Nolan 1997	Pre- and post-treatment visual acuity in each treatment group; no between-group analysis: VA change of 0.66 LogMAR units in the patching group and 0.5 LogMAR in the atropine group, time not specific (range of 2 to 9 months in patching group and 1 to 12 months in atropine group); measured using 3 different charts	NR	NR	NR	Non-adherence in the patching group was 45% compared to only 6% in the atropine group.	• No refractive change in the sound eye of any study participant • None of the 18 participants in the atropine group developed irritation of eyelids
Medghalchi 2011	Pre- and post-treatment visual acuity in each treatment group; no between-group analysis: mean VA of 0.15 LogMAR in the patching group (mean change 3.6 lines) and 0.17 LogMAR in the atropine group at 2 years; measured with Snellen chart	• 0.2 LogMAR (6/9 or 20/30 Snellen equivalent) or better = 74% of 60 participants in patching group vs 76% of 60 participants in atropine group • Worse than 0.2 LogMAR = 26% of 60 participants in patching group vs 24% of 60 participants in atropine group • "Successful treatment was defined as 2 or more lines of improvement in VA or VA of 20/25 or better in amblyopic eye" = 76% of	35% of 60 participants in patching group vs 30% of 60 participants in atropine group achieved stereo acuity of 400 second of arc at 2 years; test not specified.	NR	NR	NR

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Table 1. Outcomes reported by study *(Continued)*

		60 participants in patching group vs 74% of 60 participants in atropine group (BCVA or UCVA not specified); measured with Snellen chart				
Menon 2008	Pre- and post-treatment visual acuity in each treatment group; only report P value for between-group comparison; VA improvement from baseline of 2.38 (1.19) lines in 29 participants in patching group and 2.34 (1.14) lines in 28 participants in atropine group at 6 months; measured with ETDRS chart	NR	Pre- and post-treatment stereo acuity in each treatment group; only report P value for between-group comparison; mean stereo acuity of 746.8 (353.3) arcsec in 29 participants in patching group and 677.1 (325.3) arcsec in 28 participants in atropine group at 6 months; measured with TNO test	NR	11/29 with average adherence and 18/29 with good adherence in patching group; 12/28 with average adherence and 16/28 with good adherence in atropine group "Most patients and parents appeared to prefer atropine penalization over patching as a modality of treatment for cosmetic and psychological reasons, but this did not achieve statistical significance."	• 8/29 with itching in patching group and 5/28 in atropine group • 2/29 with redness in patching group and 8/28 in atropine group • No systemic side effects
PEDIG 2002	Mean difference between groups at 6 and 24 months (see Effects of interventions section)	Yes (see Effects of interventions section)	No difference between treatment groups in stereopsis at 24 months	"One patient in each group developed an esotropia greater than 8△ that was not present at baseline. Approximately equal numbers	Patient adherence to the occlusion protocol was documented as excellent in 49% of cases compared to 78% of cases in the atropine group. Amblyopia Treatment Index; cost for 6 months of daily patching would be about USD 100 and that for atropine would be about USD 10	Yes (see Table 2)

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Table 1. Outcomes reported by study *(Continued)*

				of patients manifested a small-angle strabismus (≤ 8△) at 6 months that was not noted at baseline and a small-angle strabismus at baseline that was not noted at 6 months; this likely reflects the variability of testing of microtropia rather than a true improvement or worsening in the ocular alignment related to treatment."		
PEDIG 2008	Difference between patching and atropine groups (adjusted for baseline VA) at 5 weeks was 0.7 (−0.9 to 2.3) letters and at 17 weeks was 1.2 (−0.7 to 3.1) letters, measured by E-ETDRS testing procedure.	• 20/32 (Snellen equivalent) or better = 26/89 in atropine group and 39/91 in patching group at 5 weeks; 36/88 in atropine group and 39/84 in patching group at 17 weeks • Worse than 20/32 (Snellen equivalent) = 63/89 in atropine group and 52/91 in patching group at 5 weeks; 52/88 in atropine group and 45/84 in patching	47/88 participants in atropine group vs 48/84 participants in patching group had stereo acuity of 400 second of arc or better at 6 months; Randot preschool stereo acuity test	"During the study, there were no differences between treatment groups in the number of participants who developed new-onset strabismus or had an increase or decrease in a preexisting strabismus"	• "Four participants received treatment that deviated from the study protocol" • "In the atropine group, patient adherence with the prescribed treatment was judged to be excellent in 52(59%), good in 22 (25%), and fair in 13 (15%) participants and poor in 1 (1%) participant. In the patching group, patient adherence was excellent in 42 (50%), good in 25 (30%), fair in 15 (18%), and poor in 2 (2%) participants." Amblyopia Treatment Index: "The questionnaire scores were similar for the atropine and patching groups on the adverse effects subscale (mean, 2.32 vs 2.27 at 5 weeks; P=.72; and mean,2.22 vs 2.28 at 17 weeks; P=.70) but low-	• "mean change in visual acuity in the sound eye from baseline was 0.3 letter in the atropine group and 1.5 letters in the patching group (mean difference between groups adjusted for baseline, 1.3 letters; 95% CI, 0.4-2.2 letters)" • "No participants were diagnosed

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Table 1. Outcomes reported by study *(Continued)*

		group at 17 weeks • 2 or more (LogMAR) lines improvement from baseline = 25/89 in atropine group and 30/91 in patching group at 5 weeks; 35/88 in atropine group and 38/84 in patching group at 17 weeks • No change (within 2 lines from baseline) = 64/89 in atropine group and 61/91 in patching group at 5 weeks; 51/88 in atropine group and 45/84 in patching group at 17 weeks • 2 or more lines loss = none at 5 weeks; 2/88 in atropine group and 1/84 in patching group at 17 weeks			er (better) for the atropine group on the social stigma treatment subscale (5-week mean, 1.91 vs 2.21; P=.03; and 17-week mean,1.91 vs 2.37; P.001) and the adherence subscale (5-week mean,2.03 vs 2.46; P=.001; and 17-week mean,2.03 vs 2.59; P.001)."	with reverse amblyopia" • "In the atropine group, ocular adverse effects, most commonly light sensitivity, were reported by 14 participants (16%). Systemic adverse effects were reported by 3 participants (3%): 1 reported tachycardia; 1, drymouth; and 1, irritability and headache. In the patching group, 4 participants (5%) had moderate to severe irritation from patching. No cases of persistent constant diplopia were reported."
Tejedor 2008	Only report P value for between-group comparison; VA improvement from baseline of 3.4 (1.4) LogMAR lines or 0.07 (0.18) LogMAR in 31 participants in atropine group and 1.8 (1.4) LogMAR lines or 0.21 (0.20) LogMAR in 32 participants in optical penalization	• 0.2 LogMAR (6/9 or 20/30 Snellen equivalent) or better = 23/31 in atropine group and 18/32 in optical penalization group • Worse than 0.2 LogMAR = 8/31 in at-	Mean stereo acuity was 447 seconds of arc in the optical penalization group and 403 seconds of arc in the atropine group (P	NR	Non-adherence was suspected in 5/32 (15.62%) of the optical penalization group and 4/31 (12.9%) of the atropine group.	1 participant in the atropine group had reverse amblyopia at 15 weeks.

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Table 1. Outcomes reported by study *(Continued)*

	group at 6 months; measured with LogMAR Crowded Glasgow acuity cards	ropine group and 14/32 in optical penalization group • 2 or more (LogMAR) lines improvement from baseline = 27/31 in atropine group and 18/32 in optical penalization group • No change (within 2 lines from baseline) = 4/31 in atropine group and 14/32 in optical penalization group • 2 or more lines loss = none	= 0.27) at 6 months; measured by Randot preschool stereo acuity test			
Yan 2008	NR	Total effective rate defined as VA 0.9 LogMAR or better, or improvement of 2 or more lines = 123/135 (91.1%) in patching group and 120/141 (85.1%) in atropine group.	NR	Change in ocular position: 18/135 increase of strabismus degree 8△ or more, 24/135 decrease of 8△ or more, 93/135 with no change in patching group; 24/141 increase of strabismus degree 8△ or more, 33/141 decrease of 8△ or more, 84/141 with no change in atropine group	Good adherence in 83.1% of patching group and 95.2% of atropine group	NR

BCVA: best-corrected visual acuity
NR: not reported
QoL: quality of life
UCVA: uncorrected visual acuity
VA: visual acuity

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Table 2. Harms of treatments at 6 months follow-up in PEDIG 2002

Reported harms	Patching n/N (%)	Atropine n/N (%)
Mild reduction in visual acuity of the sound eye not requiring treatment	17/208 (8.2%)	47/194 (24.2%)
Severe reduction in visual acuity of the sound eye requiring treatment	0/208 (0%)	1/194 (0.5%)
Mild skin irritation not requiring treatment	85/208 (41.0%)	NA
Moderate to severe skin irritation	13/208 (6.0%)	NA
Light sensitivity	NA	35/194 (18.0%)
Lid or conjunctival irritation	NA	8/194 (4.1%)
Eye pain or headaches	NA	4/194 (2.1%)
Developed strabismus	1/208 (0.5%)	1/194 (0.5%)
Ocular deviation of more than 8△	1/208 (0.5%)	1/194 (0.5%)
Among participants who had a pre-existing esotropia that increased by more than 10△	2	3
Among participants with no distance ocular deviation at baseline, a small-angle strabismus (1 to 8△) at distance fixation	12/97 (12.3%)	11/90 (12.2%)

NA: not applicable

Table 3. Harms of treatments at 17 weeks follow-up in PEDIG 2008

Reported harms	Patching n/N (%)	Atropine n/N (%)
Reverse amblyopia	0/98 (0%)	0/95 (0%)
New-onset strabismus	NA	NA
Change in pre-existing strabismus	NA	NA
Light sensitivity	0/98 (0%)	14/95 (15%)
Tachycardia	0/98 (0%)	1/95 (1%)
Dry mouth	0/98 (0%)	1/95 (1%)
Irritability	0/98 (0%)	1/95 (1%)
Headache	0/98 (0%)	1/95 (1%)
Moderate to severe itching	4/98 (4%)	0/95 (0%)
Persistent constant diplopia	0/98 (0%)	0/95 (0%)

NA: not applicable

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Amblyopia
#2 amblyop*
#3 MeSH descriptor Strabismus
#4 strabism*
#5 squint*
#6 MeSH descriptor Refractive Errors
#7 refractive near error*
#8 MeSH descriptor Anisometropia
#9 anisometropi*
#10 lazy eye*
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 occlu*
#13 patch*
#14 shield*
#15 (#12 OR #13 OR #14)
#16 MeSH descriptor Atropine
#17 atropine*
#18 (#16 OR #17)
#19 (#11 AND #15 AND #18)

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp amblyopia/
14. amblyop$.tw.
15. exp strabismus/
16. strabism$.tw.
17. squint$.tw.
18. exp refractive error/
19. (refractive adj2 error$).tw.
20. exp anisometropia/
21. anisometropi$.tw.
22. lazy eye$.tw.
23. or/13-22
24. occlu$.tw.
25. patch$.tw.
26. shield$.tw.
27. or/24-26
28. exp atropine/
29. atropine$.tw.
30. or/28-29
31. 23 and 27 and 30
32. 12 and 31

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

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Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp amblyopia/
34. amblyop$.tw.
35. exp strabismus/
36. strabism$.tw.
37. squint$.tw.
38. exp refractive error/
39. (refractive adj2 error$).tw.
40. exp anisometropia/
41. anisometropi$.tw.
42. lazy eye$.tw.
43. or/33-42
44. occlu$.tw.
45. patch$.tw.
46. shield$.tw.
47. or/44-46
48. exp atropine/
49. atropine$.tw.
50. or/48-49
51. 43 and 47 and 50
52. 32 and 51

Appendix 4. LILACS BIREME search strategy

(tw:(amblyopia or strabism$ or squint$)) AND (tw:(patch$ or occlu$ or shield$)) AND (tw:(atropine$))

Appendix 5. ISRCTN search strategy

"(Condition: amblyopia OR strabismus OR squint OR lazy eye AND Interventions: Atropine)"

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Appendix 6. ClinicalTrials.gov search strategy

(amblyopia OR strabismus OR squint OR lazy eye) AND Atropine

Appendix 7. WHO ICTRP search strategy

Condition = amblyopia OR strabismus OR squint OR lazy eye AND Intervention = atropine

WHAT'S NEW

Date	Event	Description
7 September 2018	New search has been performed	Issue 8 2019: Search updated 7 September 2018.
7 September 2018	New citation required but conclusions have not changed	Issue 8 2019: 4 new studies added to the review.

HISTORY

Protocol first published: Issue 2, 2007
Review first published: Issue 4, 2009

Date	Event	Description
16 June 2010	Amended	External source of support added.
8 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Joyce Coutu (JC), TL

Designing the review: JC, TL, KT, Argye Hillis (AH), John Flynn (JF)

Co-ordinating the review: TL, JC, RQ

Data collection for the review

- Designing electronic search strategies: CEV Information Specialist
- Undertaking electronic searches: CEV Information Specialist
- Screening search results: TL, KT, AH, RQ
- Organizing retrieval of papers: TL, RQ
- Screening retrieved papers against inclusion criteria: TL, KT, AH, RQ
- Appraising quality of papers: TL, KT, AH, RQ
- Extracting data from papers: TL, KT, AH, RQ
- Writing to authors of papers for additional information: TL
- Providing additional data about papers: TL, KT, AH
- Obtaining and screening data on unpublished studies: TL, KT

Data management for the review

- Entering data into Review Manager 5: TL, KT, RQ
- Analysis of data: TL, KT, RQ

Interpretation of data

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- Providing a methodological perspective: TL, KT, RQ
- Providing a clinical perspective: KT, JF
- Providing a policy perspective: KT, AH, JF
- Providing a consumer perspective: KT, AH

Writing the review: TL, KT, RQ
Providing general advice on the review: TL, KT, AH, JF, RQ
Securing funding for the review: TL
Performing previous work that was the foundation of the current study: TL, KT, AH, JF, JC

DECLARATIONS OF INTEREST

Tianjing Li: None known.
Riaz Qureshi: None known.
Kate Taylor: None known.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The new 'Risk of bias' table introduced by Cochrane was used to assess the methodological quality of the included studies. Post-peer review for the manuscript, a decision was made to exclude systemic therapy and therefore the search strategies were amended accordingly and the review process started again with the new search results.

INDEX TERMS

Medical Subject Headings (MeSH)

Amblyopia [*therapy]; Atropine [*therapeutic use]; Occlusive Dressings; Ophthalmic Solutions [*therapeutic use]; Randomized Controlled Trials as Topic; Visual Acuity

MeSH check words

Child; Child, Preschool; Humans

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